UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

IN RE NATIONAL PRESCRIPTION OPIATE LITIGATION This document relates to: *The County of Summit, Ohio, et al. v. Purdue Pharma L.P., et al.* Case No. 18-op-45090 *The County of Cuyahoga, Ohio, et al. v. Purdue Pharma L.P., et al.* Case No. 17-op-45004	MDL No. 2804 Case No. 17-md-2804 Hon. Dan Aaron Polster

EXPERT REPORT OF MELANIE H. ROSENBLATT, M.D.
MAY 10, 2019

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I. INTRODUCTION AND QUALIFICATIONS

A. Background and Qualifications

1. I am the Medical Director of Pain Management at Pain Management Strategies, Inc., the Medical Director of Acute Pain Management at Holy Cross Hospital, and a founding partner of Melrose Pain Strategies. Until 2017, I was the Medical Director of Pain Management for Broward Health North, a level II trauma center, where I was also the chairperson of the Credentials and Qualifications Committee and a member of the Medical Executive Board.

2. I completed my undergraduate education at the State University of New York at Stony Brook. I obtained my M.D. from the State University of New York at Stony Brook School of Medicine in 1991.

3. I completed my Anesthesiology residency and pain training at St. Joseph's Hospital Health Center in Syracuse, New York. I am board certified in Anesthesiology, Pain Management, and Addiction Medicine.

4. I have been active in several local, regional and national professional societies, including the American Society of Anesthesiologists, the Society for Pain Practice Management, the American Academy of Pain Management, and the American Society of Addiction Medicine.

5. I lecture nationally about safety and risk assessment in the treatment of chronic pain. My academic research and opinions on opioid use disorder and opioid tapering/withdrawing

have been published in Pain Medicine News and Future Medicine's Pain Management journal.[1]

6. I am an affiliate faculty member at the University of Miami as an educator in Pain Management. I was also a clinical instructor at Nova Southeastern University College of Osteopathic Medicine in the Department of Surgery.

7. I have extensive experience with the prescribing of Actiq and Fentora. This includes clinical experience gained in both the inpatient and outpatient setting. I have prescribed oral transmucosal fentanyl citrate medicines, including Actiq and Fentora, for indications listed and unlisted on the FDA-approved package insert.

8. I currently bill for my services at $600 per hour. My compensation for the work on this matter is not contingent upon the outcome of this litigation or on the content of the opinions that I offer in this case. Appendix A provides my Curriculum Vitae, which includes a list of my expert testimony within the past four years.

B. Assignment

9. I have been retained by counsel for Cephalon, Inc. ("Cephalon"), Teva Pharmaceuticals USA, Inc. ("Teva USA"), Actavis Pharma, Inc. ("Actavis Pharma"), Actavis LLC ("Actavis LLC"), Watson Laboratories, Inc. ("Watson"), and other affiliates[2] to serve as an expert witness in this case.

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[1] Pergolizzi, J. V., Jr. et al., "Tapering opioid therapy: clinical strategies," *Pain Management* Vol. 8, No. 6 (2018): 409-13.

[2] Teva USA and Cephalon are referred to as the "Teva Defendants." Actavis Pharma, Actavis LLC, Watson, Warner Chilcott Company, LLC, Actavis South Atlantic LLC, Actavis Elizabeth LLC, Actavis Mid Atlantic LLC, Actavis Totowa LLC, Actavis Kadian LLC, Actavis Laboratories UT, Inc. f/k/a Watson Laboratories, Inc.-Salt Lake City, and Actavis Laboratories FL, Inc., f/k/a Watson Laboratories, Inc.-Florida are referred to as the "Actavis Generic Defendants." In addition, I understand that Teva

10. It is my understanding that the Plaintiffs allege that the Teva Defendants engaged in off-label and other marketing that allegedly misrepresented the risks and overstated the benefits of Actiq and Fentora. Plaintiffs assert that this alleged false marketing deceived physicians into writing medically unnecessary prescriptions for Actiq and Fentora that resulted in damages associated with the opioid abuse crisis.[3]

11. I have been asked to comment on: (a) the nature of chronic non-cancer pain and breakthrough pain, (b) the suitability of opioids to treat chronic non-cancer pain and breakthrough non-cancer pain, (c) the process undergirding a physician's decision to prescribe an opioid medicine, (d) the availability of information to physicians on the risks associated with prescribing opioids, (e) whether marketing materials attributable to the Teva Defendants regarding opioid medicines, including Actiq and Fentora, are misleading or deceptive from the perspective of a licensed physician, (f) the nature of addiction and availability of information about the risk of addiction associated with Actiq, Fentora, and other opioids, (g) circumstances in which patients on opioid therapy might seek more pain relief, (h) the overall risk of misuse, abuse, and addiction associated with prescription opioids and how this risk can be mitigated, (i) the role of diversion in connection with misuse, abuse, and addiction to prescription opioids, and (j) the treatment of opioid use disorder.

Pharmaceutical Industries, Ltd. ("Teva Ltd.") has been named as a defendant in this case based upon the conduct of the Teva and Actavis Generic Defendants, but contests personal jurisdiction. Accordingly, the opinions stated herein as to the Teva and Actavis Generic Defendants also apply to Teva Ltd.

[3] Third Amended Corrected Complaint, *In Re: National Prescription Opiate Litigation*, May 29, 2018 ("Complaint"), ¶ 169.

C. Documents and Information Relied Upon

12. A list of materials I reviewed and relied upon in creating this report is attached as Appendix B. The opinions and analysis presented in this report are based on currently available information, and I reserve the right to supplement or amend this report if I receive additional information that warrants such a supplement or amendment.

II. BACKGROUND AND DEVELOPMENT OF ACTIQ AND FENTORA

13. Actiq and Fentora are oral transmucosal fentanyl citrate products (OTFCs) approved by the FDA in November 1998 and on September 25, 2006, respectively. The active pharmaceutical ingredient in both medicines is fentanyl citrate, a potent pure opioid agonist that acts primarily through interaction with opioid mu-receptors located mainly in the central nervous system.[4]

14. Before the introduction of OTFCs, anesthesiologists used fentanyl mainly at the time of surgery, and only as an injectable medication.[5] In the late 1980s, however, researchers at the University of Utah started investigating a non-injectable formulation for use in children.[6] This new formulation, OTFCs, could be rapidly absorbed through the lining of the mouth and lead to sedation before surgery. It was approved by the FDA for use in children in 1993.[7]

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[4] NIH National Cancer Institute, "Fentanyl Citrate," available at https://www.cancer.gov/publications/dictionaries/cancer-drug/def/fentanyl-citrate, accessed March 15, 2019.

[5] Stanley, Theodore H, "The fentanyl story," *The Journal of Pain* Vol. 15, No. 12 (2014): 1215-26, p. 1219.

[6] Stanley, "The fentanyl story," *The Journal of Pain* Vol. 15, No. 12 (2014): 1215-26, p. 1221.

[7] Stanley, "The fentanyl story," *The Journal of Pain* Vol. 15, No. 12 (2014): 1215-26, p. 1221.

15. Actiq is a solid formulation of fentanyl citrate attached to a plastic stick that dissolves slowly when placed in the mouth, leading to transmucosal delivery of fentanyl into the systemic circulation, and was approved for the treatment of cancer-related breakthrough pain[8] for patients aged 16 and older in 1998. Actiq was brought to market jointly by Anesta Corporation and Abbott Laboratories.[9] Cephalon has produced and marketed Actiq since its purchase of Anesta in 2000.[10]

16. Actiq's FDA-approved package insert clearly states that it is indicated "only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain."[11] The Actiq label lists the above indication and has a black-box warning that clearly reports the risks associated with using Actiq, such as "life-threatening and/or fatal respiratory depression…including following use in opioid non-tolerant patients and

[8] For a definition and discussion of "breakthrough pain," see Section V (Opinion #2) of this report.

[9] Anesta Corporation and Abbott Laboratories, "Actiq Risk Management Program," November 4, 1998, TEVA_MDL_A_00564336-65.

[10] Cephalon also purchased the marketing rights for Actiq from Abbott Laboratories in 2000. *See* Cephalon, Inc., Form 10-K405, filed March 30, 2001, p. 31.

[11] This quote is from the first Actiq label to be approved, "Actiq Label, November 1998," 1998, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/20747lbl.pdf. The most recently approved Actiq Label is "Actiq Label, December 2016," 2016, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020747s043s044lbl.pdf. It states that is indicated "for the management of breakthrough pain in cancer patients 16 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain." This 2016 label characterizes opioid tolerant patients as "those who are taking around-the-clock medicine consisting of at least 60mg of oral morphine daily, at least 26 mcg of transdermal fentanyl/hour, at least 30mg of oral oxycodone daily, at least 8mg of oral hydromorphone daily, at least 25 mg oral oxymorphone daily, or an equianalgesic does of another opioid daily for a week or longer."

improper dosing."[12] This warning also indicates that Actiq is "contraindicated [...] in the management of acute or postoperative pain."[13]

17. In 2006, Fentora, an oral transmucosal buccal tablet of fentanyl citrate, was approved by the FDA "for the management of breakthrough pain in cancer patients 18 years of age or older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain."[14] Like Actiq, Fentora's black-box warning has always explained that the medication is contraindicated in patients who are "opioid non-tolerant."[15] The warning also states that Fentora should only be prescribed by "healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain."[16] The label for Fentora makes clear the warnings associated with these medicines, particularly "respiratory depression," "addiction, abuse, and misuse."[17]

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[12] "Actiq Label, December 2016."

[13] "Actiq Label, November 1998." The most recent label phrases this as "Not for use in opioid non-tolerant patients" and directs physicians to the TIRM REMS Access program for additional information: "Healthcare professionals who prescribe ACTIQ on an outpatient basis must enroll in the TIRF REMS Access program and comply with the requirements of the REMS to ensure safe use of ACTIQ." "Actiq Label, December 2016."

[14] Rappaport, Bob, "FDA Approval Letter for Fentora," September 25, 2006, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/021947s000ltr.pdf. The original Fentora label is "Fentora Label, September 2006," 2006, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021947lbl.pdf.

[15] "Fentora Label, September 2006"; "Actiq Label, November 1998." The most recently approved Fentora label is "Fentora Label, April 2017," 2017, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021947s019lbl.pdf. It maintains this warning that it is "Not for use in opioid non-tolerant patients."

[16] "Fentora Label, September 2006." The most recent label notes that fentanyl is a Schedule II controlled substance and explains that "fentanyl buccal tablets are available only through a restricted program called the TIRF REMS Access program," which includes "review[ing] the prescriber educational materials for the TIRF REMS Access program, enroll[ing] in the program, and comply[ing] with the REMS requirements." "Fentora Label, April 2017."

[17] "Fentora Label, April 2017"; The 2006 Fentora label warns of "misuse, and criminal diversion" and "abuse and addiction." "Fentora Label, September 2006," p. 12.

III. SUMMARY OF OPINIONS

18. I have reached the following conclusions to a reasonable degree of certainty.

19. Chronic non-cancer pain ("CNCP") is pervasive and serious and often requires medical intervention.

20. Breakthrough pain is serious and debilitating, and is experienced by a sub-set of CNCP patients.

21. For patients who are properly screened and monitored, the administration of opioids can be an appropriate treatment of CNCP. In particular, Actiq and Fentora may be appropriate treatments of breakthrough non-cancer pain.

22. A physician's decision whether to prescribe Actiq, Fentora, or any other opioid for the treatment of CNCP (breakthrough pain or otherwise) should be based on an individualized assessment of patient- and pain-specific factors.

23. Prior to prescribing Actiq or Fentora, prescribers should consider each medicine's associated risks. Further, prescribers are required to review a medication guide with patients, sign a provider-patient agreement, and comply with the other requirements of the transmucosal immediate-release fentanyl ("TIRF") Risk Evaluation and Mitigation Strategy ("REMS") Program.

24. Marketing materials and sponsored research can be useful sources of information for physicians. The Actiq and Fentora marketing materials I reviewed are consistent with their respective labels and are not misleading or deceptive; likewise, the third-party publications I reviewed are not misleading or deceptive when read as a whole.

25. Addiction is a risk not only of opioids but also of numerous medications and is the result of many factors, including biological predisposition. Moreover, physicians have long known of the addiction risks associated with opioid medicines like Actiq or Fentora.

26. There is a distinction between addiction and dependence. In my experience, some patients who are on opioid therapy may appear to engage in drug-seeking behaviors simply because of their legitimate need for additional pain relief.

27. Actiq and Fentora have a well-known, acceptable, and manageable risk of misuse, abuse, and addiction when prescribed properly to treat breakthrough pain in CNCP and in conjunction with thorough screening, monitoring and frequent assessment.

28. Many people who misuse, abuse, or become addicted to prescription opioids obtained them improperly – without a valid prescription.

29. Opioid use disorder (OUD) can be treated effectively through pharmacologic and non-pharmacologic methods.

IV. OPINION #1: CHRONIC NON-CANCER PAIN ("CNCP") IS PERVASIVE AND SERIOUS, AND OFTEN REQUIRES MEDICAL INTERVENTION.

30. Chronic pain, a term used to describe ongoing or recurrent pain lasting beyond the usual course of acute illness or injury, is pervasive and serious, and imposes significant costs on both the individual suffering from it and on society at large.[18] The International Association for the Study of Pain defines chronic pain as "pain that persists beyond

[18] American Chronic Pain Association, "ACPA Resource Guide to Chronic Pain Management: An Integrated Guide to Medical, Interventional, Behavioral, Pharmacologic and Rehabilitation Therapies," 2018, available at https://www.theacpa.org/wp-content/uploads/2018/03/ACPA_Resource_Guide_2018-Final-v2.pdf.

normal tissue healing time, which is assumed to be three months."[19] Chronic pain is classified by pathophysiology as nociceptive, neuropathic, or a mixture of these.[20] About 100 million adults in the United States are affected by chronic pain at any given time.[21] Chronic pain is therefore recognized as an important and often undertreated public health problem.[22] It can be devastating.

31. There are two central classifications of chronic pain: nociceptive and neuropathic pain. Nociceptive pain is caused by potentially harmful stimuli such as inflammation or tissue damage and is further subdivided into visceral and somatic pain. Sensations related to nociceptive pain vary depending on the locus of pain and its cause but range from "localized stabbing" and "aching" to "vague, diffuse cramping, or nausea."[23] Neuropathic pain, on the other hand, stems from abnormal processing by the peripheral or central nervous system, with sensations ranging from "sharp, stabbing" to "tingling" and "numbness."[24] A plethora of pain syndromes and inflammatory disorders can cause

[19] Intermountain Healthcare, "Management of Chronic Non-Cancer Pain," 2012, available at https://intermountainhealthcare.org/ext/Dcmnt?ncid=521023323.

[20] Intermountain Healthcare, "Management of Chronic Non-Cancer Pain."

[21] Gaskin, Darrell J and Patrick Richard, "The economic costs of pain in the United States," *The Journal of Pain* Vol. 13, No. 8 (2012): 715-24.

[22] Goldberg, Daniel S. and Summer J. McGee, "Pain as a Global Public Health Priority," *BMC Public Health* Vol. 11, No. 1 (2011): 770-75; CDC, "Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults – United States, 2016," *Morbidity and Mortality Weekly Report*, Vol. 67, No. 36 (September 14, 2018): pp. 1001-1006 ("In 2016, an estimated 20.4% of U.S. adults had chronic pain and 8.0% of U.S. adults had high-impact chronic pain. Both were more prevalent among adults living in poverty, adults with less than a high school education, and adults with public health insurance.").

[23] Intermountain Healthcare, "Management of Chronic Non-Cancer Pain." In my experience, nausea is typically associated with visceral pain.

[24] Intermountain Healthcare, "Management of Chronic Non-Cancer Pain."

chronic pain of either type. Common examples of these are osteoarthritis, rheumatoid arthritis, diabetic peripheral neuropathy, and post-herpetic neuralgia.[25]

32. Because chronic pain can be caused by a wide variety of conditions, physicians certified in many different specialties are accustomed to and experienced with treating chronic pain patients. This includes oncologists, rheumatologists, neurologists, anesthesiologists, and physical and occupational therapy specialists.[26]

33. Chronic pain, whether cancer or non-cancer related, poses a substantial biological, emotional, economic, and social burden. One systematic survey of the literature related to CNCP suggests that about one-half of individuals with CNCP exhibit physical deterioration and limited ability to perform daily activities.[27] Moreover, the same review found that CNCP leads to absenteeism and/or lower efficiency in working-age patients, which, in turn, leads to reduced economic well-being. There is also ample evidence of CNCP's negative effect on patients' mental health and quality of life, either directly or as a by-product of its impact on physical and economic health. Individuals with CNCP are at higher risk of suicide than their non-CNCP counterparts.[28] Indeed, as physicians have sharply limited chronic pain patients' access to opioids in recent years, news articles have

[25] Intermountain Healthcare, "Management of Chronic Non-Cancer Pain."

[26] WebMD, "8 Specialists Who Treat Pain," available at https://www.webmd.com/back-pain/guide/pain-specialists#2, accessed April 26, 2019; American RSDHope, "Medical Articles - Your Doctor and You," available at http://www.rsdhope.org/your-doctor-and-you.html, accessed April 26, 2019.

[27] Dueñas, María et al., "A review of chronic pain impact on patients, their social environment and the health care system," *Journal of Pain Research* Vol. 9 (2016): 457-61.

[28] Cheatle, Martin D et al., "Prevalence of suicidal ideation in patients with chronic non-cancer pain referred to a behaviorally based pain program," *Pain Physician* Vol. 17, No. 3 (2014): E359-67.

begun to report at least dozens of suicides directly linked to their suddenly under-treated pain due to the forced taper leading to withdrawal symptoms.[29]

V. OPINION #2: BREAKTHROUGH PAIN IS SERIOUS AND DEBILITATING AND IS EXPERIENCED BY A SUBSET OF CNCP PATIENTS.

34. In my experience, patients suffering from CNCP can also experience "breakthrough pain," defined as the "transient pain exacerbation in patients with stable and controlled basal pain."[30] In other words, breakthrough pain is a more severe manifestation of a patient's already-existing chronic pain, and is recognized in pain research for cancer pain as well as CNCP.[31] Researchers recognize several types of breakthrough pain: the "incidental type involves flares of pain associated with movement or activity; idiopathic

[29] "How the opioid crackdown is backfiring," 2018, available at https://www.politico.com/story/2018/08/28/how-the-opioid-crackdown-is-backfiring-752183, accessed May 1, 2019; Szalavitz, Maia, "When the Cure is Worse than the Disease," *The New York Times* February 9, 2019; Llorente, Elizabeth, "As doctors taper or end opioid prescriptions, many patients driven to despair, suicide," December 10, 2018, available at https://www.foxnews.com/health/as-opioids-become-taboo-doctors-taper-down-or-abandon-pain-patients-driving-many-to-suicide, accessed May 1, 2019.

[30] Margarit, Cesar et al., "Breakthrough cancer pain–still a challenge," *Journal of Pain Research* Vol. 5 (2012): 559.

[31] See, e.g. Caraceni, Augusto et al., "Guidelines for the management of breakthrough pain in patients with cancer," *Journal of the National Comprehensive Cancer Network* Vol. 11, Supplement 1 (2013): S-29-S-36; Mercadante, Sebastiano et al., "Episodic (breakthrough) pain: consensus conference of an expert working group of the European Association for Palliative Care," *Cancer* Vol. 94, No. 3 (2002): 832-39; Mercadante, Sebastiano et al., "Factors influencing the use of opioids for breakthrough cancer pain: A secondary analysis of the IOPS-MS study," *European Journal of Pain* Vol. 23, No. 4 (2018): 719-26; Payne, Richard, "Recognition and diagnosis of breakthrough pain," *Pain Medicine* Vol. 8, Supplement 1 (2007): S3-S7; Portenoy, Russell K et al., "Breakthrough pain in community-dwelling patients with cancer pain and noncancer pain, part 1: prevalence and characteristics," *Journal of Opioid Management* Vol. 6, No. 2 (2010): 97-108; Rudowska, Joanna, "Management of breakthrough pain due to cancer," *Contemporary Oncology* Vol. 16, No. 6 (2012): 498-501, p. 1; Slatkin, Neal E. and Rhiner, Michele I., "Breakthrough Pain: Improving Recognition and Management to Enhance Quality of Life," 2008, available at www.medscape.org/viewarticle/572129, accessed October 10, 2017; Smith, Howard, "A comprehensive review of rapid-onset opioids for breakthrough pain," *CNS Drugs* Vol. 26, No. 6 (2012): 509-35; Taylor, Donald R et al., "Impact of breakthrough pain on quality of life in patients with chronic, noncancer pain: Patient perceptions and effect of treatment with oral transmucosal fentanyl citrate (OTFC®, ACTIQ®)," *Pain Medicine* Vol. 8, No. 3 (2007): 281-88; Webster, Lynn R and M. Beth Doveh, "Optimizing Opioid Treatment for Breakthrough Pain," 2007, available at www.medscape.org/viewarticle/563417, accessed October 10, 2017.

type is transitory pain unrelated to a specific activity; and end-of-dose failure pain occurs when blood levels of medications fall below an analgesic threshold at the end of a dosing interval."[32] Breakthrough pain "often occurs in patients with cancer, but… can also occur in chronic disease patients with pain."[33] Breakthrough pain has been studied extensively, including in patient populations with and without cancer.[34]

35. One study from 2012 asked CNCP patients to describe their breakthrough pain. These patients reported, on average, six episodes of breakthrough pain per day with durations of up to nearly two hours.[35] In this study, surveyed patients characterized breakthrough pain as more intense than their chronic pain, with "sharp," "shooting," and "stabbing" being common descriptors.[36] A survey of 228 patients in 2006 found that 74% of CNCP patients experienced severe-to-excruciating breakthrough pain.[37]

36. Undertreated breakthrough pain in CNCP patients can be devastating. Undertreated breakthrough pain in general imposes not only direct costs, such as additional clinical

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[32] Rudowska, "Management of breakthrough pain due to cancer," p. 1.

[33] Slatkin, "Breakthrough Pain: Improving Recognition and Management to Enhance Quality of Life."

[34] See, e.g. Portenoy et al., "Prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain," *The Journal of Pain* Vol. 7, No. 8 (2006): 583-91, ("This article presents results from a survey that demonstrates that breakthrough pain is highly prevalent and varied in opioid-treated patients with chronic noncancer pain"); Portenoy et al., "Breakthrough pain in community-dwelling patients with cancer pain and noncancer pain, part 1: prevalence and characteristics," *Journal of Opioid Management* Vol. 6, No. 2 (2010): 97-108; Payne, "Recognition and diagnosis of breakthrough pain," *Pain Medicine* Vol. 8, Supplement 1 (2007): S3-S7, p.S4 ("In a recent survey of 228 patients with noncancer pain, 74% had BTP"); Smith, "A comprehensive review of rapid-onset opioids for breakthrough pain," *CNS Drugs* Vol. 26, No. 6 (2012): 509-35, p. 510 ("BTP is highly prevalent in certain patient populations, occurring in 33-55% of patients with chronic cancer pain and ~70% of patients with chronic noncancer pain").

[35] Guarino, Anthony and Martha Cornell, "Breakthrough Pain in Non-Cancer Patients," *Practical Pain Management* Vol. 6, No. 3 (2012): 1-5.

[36] Guarino, "Breakthrough Pain in Non-Cancer Patients," *Practical Pain Management* Vol. 6, No. 3 (2012): 1-5.

[37] Portenoy et al., "Prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain," *The Journal of Pain* Vol. 7, No. 8 (2006): 583-91.

treatment time, but also indirect costs. These indirect costs can include "lost income as a result of time taken off work for a [breakthrough pain] episode, a spouse's or caregiver's lost income because of time off work, or the expense of extra household help[, ...] the patient's pain, suffering, depression, anxiety, loss of sleep, and fatigue, as well as the family's and/or caregiver's distress."[38] Cancer patients with breakthrough pain have also been found to require more pain-related hospitalizations and physician office visits, leading to increased medical costs.[39] This is also consistent with my experience working with CNCP patients who have suffered from untreated or under-treated breakthrough pain.

VI. OPINION #3: OPIOIDS MAY BE AN APPROPRIATE TREATMENT OF CNCP FOR PATIENTS WHO ARE APPROPRIATELY SCREENED AND MONITORED. IN PARTICULAR, ACTIQ AND FENTORA MAY BE APPROPRIATE TREATMENTS OF BREAKTHROUGH CNCP FOR OPIOID-TOLERANT PATIENTS WHO ARE APPROPRIATELY SCREENED AND MONITORED.

37. Opioids have been used for the treatment of a variety of painful conditions, including acute pain following trauma or surgery, cancer-related pain, and CNCP.

[38] Abernethy, Amy P, Jane L Wheeler, and Barry V Fortner, "A health economic model of breakthrough pain," *American Journal of Managed Care* Vol. 14, No. 5, Supplement 1 (2008): S129-40.

[39] Fortner, Barry V, Theodore A Okon, and Russell K Portenoy, "A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain," *The Journal of Pain* Vol. 3, No. 1 (2002): 38-44; Fortner, Barry V et al., "Description and Predictors of Direct and Indirect Costs of Pain Reported by Cancer Patients," *Journal of Pain and Symptom Management,* Vol. 25, No. 1 (2003): pp. 9-18, pp. 14-16 ("The presence of breakthrough pain was a significant predictor of direct pain-related costs [...] indicating that patients with breakthrough pain incurred higher direct pain-related costs [...] than patients without breakthrough pain. [...] The presence of breakthrough pain predicted higher indirect pain-related costs. [...] Pain intensity, pain interference, and presence of breakthrough pain predicted higher indirect expenses, suggesting that as pain intrudes on the daily lives of cancer patients they begin to incur expenses for issues outside of direct medical treatment of pain").

38. Short-acting opioids work to control pain regardless of the etiology of the pain. When used in combination with long-acting opioids, short-acting opioids are used to manage breakthrough pain. When short-acting opioids are used alone (not in combination with long-acting opioids), they can be effective for treating breakthrough pain, when a patient prefers to not be on opioids "around-the-clock." For example, patients may prefer not to be on opioids during the day when they have to be at work or need to care for children. In my experience, I have also found that people whose job consists of driving (e.g., delivery drivers, couriers, truck drivers) prefer not to be on opioid therapy while driving. Some of my patients experience more pain than usual after a particularly active day. In these circumstances, patients may benefit from short-acting opioids taken on an as-needed basis.

39. Long-acting opioids work continuously and are indicated for the management of chronic pain when other alternatives have failed and for which around-the-clock pain relief is needed.[40] Prescribing long-acting opioids can benefit a patient in a number of ways, including, but not limited to, maintaining a constant level of medication in the body, potentially preventing pain recurrence, and minimizing feelings of euphoria and/or withdrawal. Furthermore, patients may find it easier to comply with prescribing instructions for long-acting opioids, as they are associated with fewer administrations per day relative to short-acting opioids.

40. In my own practice, opioids play an important role in the chronic pain armamentarium. For example, when treating patients with chronic pain with no history of substance abuse,

[40] Ray, James B, "Implications of the extended-release/long-acting opioid REMS for managed care," *American Journal of Managed Care* Vol. 21 (2015): S177a-S187a.

I have found that some patients who remain in severe, debilitating pain following non-opioid treatment (such as ice, heat, or physical therapy) benefit from a trial of opioid therapy. In general, the suitability of long-acting opioids for chronic pain depends on the nature and intensity of a patient's pain, the patient's therapeutic goals, and the expected impact of treatment on his or her quality of life. Two patients suffering from similar levels of chronic pain may well benefit from different treatment strategies. The choice of non-opioid therapy for one does not diminish the potential efficacy of opioid therapy for the other. Many opioids have been and continue to be approved for the treatment of CNCP.[41]

41. Plaintiffs' experts appear to take different views on whether it is appropriate to use opioids to treat CNCP. Most agree that opioids have an important role to play in treating pain, but there is more variety in opinions about which cases are appropriate. I agree with Dr. Schumacher that opioids can be appropriate for treating conditions "such as pain from advanced multiple sclerosis, sickle cell disease, pain following spinal cord injury and paraplegia, or post-herpetic neuralgia [...as a] a third-line therapy" after other treatments have been attempted.[42] I also agree that opioids "have an integral role in the current practice of medicine," "have long been used successfully for the management of acute pain," and are appropriate for certain patients suffering from CNCP.[43] Other experts,

[41] Examples include Hysingla ER, Zohydro ER, or Vicodin. Hysingla ER's indications, for example, include "the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate." "Hysingla ER Label, September 2018," 2018, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206627s007s008lbl.pdf.

[42] Expert Report of Mark A. Schumacher, M.D., Ph.D., *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019 ("Schumacher Report"), ¶ 86.

[43] Schumacher Report, at ¶¶ 86, 121, 140.

such as Dr. Lembke, assert that opioids have little to no role in treating chronic pain.[44] This wide disparity in the opinions of Plaintiffs' experts mirrors the wide range of opinions in the medical field. In my experience, strategies to manage chronic pain vary widely whereas strategies to manage other chronic medical conditions are generally more standardized.[45]

42. I agree that opioids carry significant safety risks, which are disclosed in the labels for the medicines and which are taught to all physicians in the course of their medical school and training. I also agree that opioids should not be the first-line treatment for CNCP or cancer pain. Nonetheless, opioids can be effective in treating CNCP, based upon my experience treating thousands of patients, both inpatient and outpatient, for acute and chronic pain.

43. Although non-pharmacologic and non-opioid pharmacologic therapies are preferred for both acute and chronic pain, opioids may be considered for patients that fail to respond to these more conservative therapies. In general, I use a multimodal approach to pain treatment that includes non-pharmacologic as well as non-opioid and opioid therapy. In doing so, I approach pain from multiple pathways (e.g., ice, heat, physical therapy, interventional pain techniques) and assess patient response. Depending on a patient's specific conditions, I sometimes try non-opioid medication as well, including muscle

[44] Expert Report of Anna Lembke, M.D., *In Re National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019 ("Lembke Report"), p. 5 ("Limiting opioid prescribing is good medicine, because it decreases exposure to a dangerous and potentially lethal drug, without compromising pain treatment. [...] there is insufficient evidence that long-term opioid therapy effectively treats chronic pain.").

[45] An article published by Multiple Chronic Conditions Resource Center suggests that "[b]ecause pain tolerance is different for every individual, there is no one-size-fits-all approach to chronic pain management." *See* Multiple Chronic Conditions Resource Center, "Chronic Pain Guidelines," available at https://www.multiplechronicconditions.org/chronic-pain-guidelines.

relaxants, anti-inflammatories, antidepressants, and anticonvulsants. When prescribing opioids as part of this comprehensive approach, I begin treatment with the lowest effective dose then continually assess the risks/benefits and monitor for side effects. Although there is no single formula or protocol for appropriate opioid prescribing, it is generally not acceptable to simply escalate the dose until side effects become problematic. Instead, I take into account the totality of each patient's response to multimodal therapy in making changes to their medications, as well as the risks and potential benefits of that such therapy.

A. Off-label Prescribing May be Appropriate for Treating CNCP

44. Physicians often use medications for purposes other than the FDA-approved indication.[46] This includes numerous medications that have been or are used for the treatment of pain, such as amitriptyline, trazodone, desipramine, imipramine, venlafaxine, gabapentin, oxcarbazepine, topiramate, or transdermal lidocaine patch. Many of these medicines were approved with a limited pain-related indication or no pain indication at all, but are frequently prescribed for off-label indications in patients experiencing CNCP. For example, trazodone, which is indicated only "for the treatment of major depressive disorder," can be an effective adjuvant for CNCP as well as comorbid anxiety, insomnia and depression.[47]

[46] A report of off-label prescribing patterns of US office-based physicians documented that 46% of prescriptions for cardiac and anticonvulsant medications were for off-label indications. Radley, David C, Stan N Finkelstein, and Randall S Stafford, "Off-label prescribing among office-based physicians," *Archives of Internal Medicine* Vol. 166, No. 9 (2006): 1021-26.

[47] Substance Abuse and Mental Health Services Administration (SAMHSA), "Managing Chronic Pain in Adults With or in Recovery from Substance Use Disorders," 2012, available at

45. Examples of common off-label use of medications in patients with pain include the use of gabapentin for a wide variety of neuropathic pain conditions, even though gabapentin is indicated only for the management of postherpetic neuralgia and epilepsy in adults.[48] Gabapentin has also been used as part of multi-modal pain therapy in patients following surgery. Tricyclic antidepressants have been used as a co-analgesic for the treatment of a wide variety of painful conditions, including fibromyalgia, neuropathic pain (including postherpetic neuralgia and painful diabetic peripheral neuropathy), and chronic low back pain.

B. Opioids May be an Appropriate Treatment for Breakthrough Pain

46. Patients who take around-the-clock opioids for CNCP often report experiencing breakthrough pain, including "end-of-dose failure" pain. Breakthrough pain occurs in approximately 50% of outpatients with both cancer and non-cancer pain.[49] Published clinical guidelines on the use of opioids for the treatment of CNCP recognize that breakthrough pain can occur in patients suffering from non-cancer pain.[50]

47. Breakthrough pain can be treated using rapid-acting opioids such as TIRFs. Actiq and Fentora are examples of TIRFs. These transmucosal opioids can be administered via

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https://store.samhsa.gov/system/files/sma13-4671.pdf; "Trazodone Label," 2015, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/071196s062lbl.pdf.

[48] "Neurontin (Gabapentin) Label," 2017, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020235s064_020882s047_021129s046lbl.pdf.

[49] Rudowska, "Management of breakthrough pain due to cancer," *Contemporary Oncology* Vol. 16, No. 6 (2012): 498-501, p. 1; Portenoy et al., "Breakthrough pain in community-dwelling patients with cancer pain and noncancer pain, part 1: prevalence and characteristics," *Journal of Opioid Management* Vol. 6, No. 2 (2010): 97-108.

[50] Chou, Roger et al., "Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain," *The Journal of Pain* Vol. 10, No. 2 (2009): 113-30.e22, pp. 122-123.

intranasal sprays, sublingual sprays, and sublingual tablets. TIRFs become active within minutes and have a duration of 1-2 hours, which correspond well to the time course of breakthrough pain. Longer-acting opioids may not be as effective for managing breakthrough pain due to their delayed onset, as there is an urgency to treating breakthrough pain. TIRFs can be also beneficial for those who do not tolerate oral medications. During end-of-life care, up to 70% of patients require a non-oral route of opioid administration. Buccal absorption from crushed pills can pose a choking hazard (and are not indicated for use in this manner). Thus, TIRFs are a noninvasive, effective, and efficient way of administering pain relief.[51] As noted above, physicians must weigh the potential benefits with risks of harm when considering the use of rapid-acting opioids for the treatment of breakthrough pain in patients.

48. Studies have found that TIRFs (including sublingual sprays and sublingual fentanyl tablets) are efficacious in treating breakthrough cancer and non-cancer pain in patients who are opioid tolerant.[52] Patients with chronic cancer and non-cancer pain have been

[51] Chang, Andrew et al., "Transmucosal immediate-release fentanyl for breakthrough cancer pain: opportunities and challenges for use in palliative care," *Journal of Pain & Palliative Care Pharmacotherapy* Vol. 29, No. 3 (2015): 247-60.

[52] See, e.g. Shimoyama, N. et al., "Efficacy and safety of sublingual fentanyl orally disintegrating tablet at doses determined from oral morphine rescue doses in the treatment of breakthrough cancer pain," *Japanese Journal of Clinical Oncology* Vol. 45, No. 2 (2014): 189-96; Nalamachu, Srinivas et al., "Long-term effectiveness and tolerability of sublingual fentanyl orally disintegrating tablet for the treatment of breakthrough cancer pain," *Current Medical Research and Opinion* Vol. 27, No. 3 (2011): 519-30; Minkowitz, Harold et al., "Long-term safety of fentanyl sublingual spray in opioid-tolerant patients with breakthrough cancer pain," *Supportive Care in Cancer* Vol. 24, No. 6 (2016): 2669-75; Mercadante et al., "Factors influencing the use of opioids for breakthrough cancer pain: A secondary analysis of the IOPS-MS study," *European Journal of Pain* Vol. 23, No. 4 (2018): 719-26; Webster, Lynn R et al., "Fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic cancer and noncancer pain: a randomized, double-blind, crossover study followed by a 12-week open-label phase to evaluate patient outcomes," *Pain Medicine* Vol. 14, No. 9 (2013): 1332-45; Ashburn, Michael A et al., "The efficacy and safety of fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic pain," *Anesthesia & Analgesia* Vol. 112, No. 3 (2011): 693-702; Taylor et al., "Impact of breakthrough pain on quality of life in patients with chronic, noncancer pain: Patient perceptions and effect

found to prefer fentanyl buccal tablets over oxycodone, and both patients and clinicians have reported better functional improvements with fentanyl buccal tablets, versus other short-acting opioids.[53] Patients with chronic pain have also reported greater pain reduction after fentanyl buccal tablets versus oxycodone.[54]

49. In particular, clinical studies have also found that Actiq and Fentora are effective in treating breakthrough pain. One study of the effect of treatment with OTFC medicines found that Actiq (and similar medications) resulted in substantial improvement in several quality of life metrics, including "general activity level."[55] Another study found that Actiq yielded significantly better pain reduction than immediate-release morphine sulfate in those with breakthrough cancer pain.[56]

50. A study of the effects and potential adverse impacts of fentanyl buccal tablets (including Fentora) concluded that they were "generally safe and well tolerated, with self-reported

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of treatment with oral transmucosal fentanyl citrate (OTFC®, ACTIQ®)," *Pain Medicine* Vol. 8, No. 3 (2007): 281-88; Fine, Perry G et al., "Long-term safety and tolerability of fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic pain: an 18-month study," *Journal of Pain and Symptom Management* Vol. 40, No. 5 (2010): 747-60.

[53] Webster et al., "Fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic cancer and noncancer pain: a randomized, double-blind, crossover study followed by a 12-week open-label phase to evaluate patient outcomes," *Pain Medicine* Vol. 14, No. 9 (2013): 1332-45.

[54] Ashburn et al., "The efficacy and safety of fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic pain," *Anesthesia & Analgesia* Vol. 112, No. 3 (2011): 693-702.

[55] Taylor et al., "Impact of breakthrough pain on quality of life in patients with chronic, noncancer pain: Patient perceptions and effect of treatment with oral transmucosal fentanyl citrate (OTFC®, ACTIQ®)," *Pain Medicine* Vol. 8, No. 3 (2007): 281-88.

[56] Coluzzi, Paul H et al., "Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC®) and morphine sulfate immediate release (MSIR®)," *Pain* Vol. 91, No. 1-2 (2001): 123-30.

functional improvement observed in most of the opioid-tolerant patients with [breakthrough pain] in association with chronic noncancer pain."[57]

51. The labels for Actiq and Fentora state that these opioid medicines are indicated for the "management of breakthrough pain" in cancer patients who are already tolerant to opioid therapy for their underlying persistent cancer pain.[58] It may also be medically appropriate to prescribe OTFC medicines, such as Actiq and Fentora, for off-label purposes based on existing clinical practice guidelines, following a careful review of the patient's medical history, a physical examination, and a clear explanation of the risks.

52. The studies outlined above provide evidence that these medicines are effective in providing pain relief, and there are many cases where Actiq and Fentora might be particularly well-suited to addressing a patient's needs. For example, a spinal cord injury patient with a tracheotomy might benefit from a transdermal fentanyl patch, with Fentora or Actiq for breakthrough pain. Similarly, patients who do not tolerate oral medication (due to gastrointestinal upset, ulcers, difficulty swallowing, or other reasons) might also benefit. If the patient feels too sedated on the transdermal fentanyl patch, he or she might still benefit by using Fentora or Actiq alone. Withholding pain medication that is potentially medically appropriate could lead to unnecessary suffering on the part of the patient.[59]

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[57] Fine et al., "Long-term safety and tolerability of fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic pain: an 18-month study," *Journal of Pain and Symptom Management* Vol. 40, No. 5 (2010): 747-60.

[58] "Actiq Label, November 1998"; "Actiq Label, December 2016"; "Fentora Label, September 2006"; "Fentora Label, April 2017."

[59] *See* Deposition of Dr. Russell Portenoy, January 24, 2019 ("Portenoy Deposition"), at p. 304:4 to p.304:12, ("Q. So even today for the use of opioids to treat chronic pain associated with cancer is still less than where the

VII. OPINION #4: THE DECISION WHETHER TO PRESCRIBE AN OPIOID, INCLUDING ACTIQ OR FENTORA, SHOULD BE BASED ON AN INDIVIDUALIZED INQUIRY OF NUMEROUS PATIENT- AND PAIN-SPECIFIC FACTORS.

53. A prescriber's decision to include opioid medications in a treatment plan must be made on a patient-by-patient basis, after balancing the risks of harm with the potential benefits.

54. The decision to use short-acting opioids, including Actiq and Fentora, for the treatment of breakthrough pain is no different. The potential benefits include decreased pain intensity and improved physical and mental functioning, but at the risk of opioid-induced adverse events, possibly including increased risk of misuse, abuse, and diversion.[60]

55. Faced with these potential benefits and risks, health care providers deciding whether to prescribe Actiq and Fentora for any use (on-label or off-label) must exercise their independent professional, medical judgment. Such judgment may be based upon many different factors. These include, among other things, their medical training and experience; their specific experiences with Actiq and Fentora; their exposure to and understanding of the scientific literature regarding Actiq, Fentora, and similar opioid medication; their evaluation of the risk-benefit profile for the patient; the medical history of the patient including any history of substance abuse; the treatment history of the patient, including whether the patient has tried and failed alternative therapies, or whether the patient has had past success with Actiq and Fentora and is seeking a refill; direct input from the patient; appropriate monitoring for aberrant behaviors including urine drug

scientific literature would suggest it needs to be; is that correct? A. Yes. Q. And you believe that is a detriment to patients who are suffering from pain who are not being adequately treated? A. Yes, I do.").

[60] "Actiq Label, December 2016"; "Fentora Label, April 2017."

screening and Prescription Drug Monitoring Programs (PDMP) review; review of adverse events; and influence by third party payers, such as insurance companies [61] Of course, over time, that judgment may shift, even for the same patient, depending on particular circumstances.

56. In my practice, the decision to recommend Actiq or Fentora for breakthrough pain in CNCP is based on my clinical judgment following a careful review of the patient's medical history and physical examination that lead to a clinical diagnosis and, in turn, the generation of an individualized treatment plan. Ongoing monitoring of patients is a vital component to managing pain in complex patients who require opioid therapy.

57. When assessing a patient for opioid therapy, physicians should be aware of the Centers for Disease Control (CDC) and State-specific guidelines. [62] It is my understanding that

[61] Plaintiffs' experts have recognized that "there are a lot" of factors other than marketing that influence doctors to prescribe medicines. Deposition of David Cutler, Ph.D., *In Re: National Prescription Opiate Litigation* MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, April 26, 2019, pp. 182-185 ("Q. [... H]ave you studied the different factors that motivate doctors to write prescriptions, or the variations in treatment among particular doctors? [...] A. [O]ne of the factors that enters into physicians' prescriptions is their own belief about effectiveness. [...] Q. Okay. Would you agree that physicians are also motivated by prescribing standards of care in terms of determining what types of prescriptions they write? A. In general there are a lot of influences on physicians. [...] Q. And patient preference also impacts a doctor's motivations to write prescriptions, right? [...] A. [... T]he economic literature does suggest that patient preferences are important, although the economic literature suggests that physician factors are far more important").

[62] For a summary of the CDC guidelines, *see* Dowell, Deborah, Tamara M. Haegerich, and Roger Chou, "CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016," *Morbidity and Mortality Weekly Report* Vol. 65, No. 1 (2016): 1-49. The CDC issued an update in 2019 advising against the misapplication of the 2016 guidelines, see Centers for Disease Control and Prevention, "CDC Advises Against Misapplication of the Guideline for Prescribing Opioids for Chronic Pain," 2019, available at https://www.cdc.gov/media/releases/2019/s0424-advises-misapplication-guideline-prescribing-opioids.html, accessed April 26, 2019 ("CDC commends efforts by healthcare providers and systems, quality improvement organizations, payers, and states to improve opioid prescribing and reduce opioid misuse and overdose. However, some policies and practices that cite the Guideline are inconsistent with, and go beyond, its recommendations. [...] [P]olicies that mandate hard limits conflict with the Guideline's emphasis on individualized assessment of the benefits and risks of opioids given the specific circumstances and unique needs of each patient.").

Examples of state guidelines include: Governor's Cabinet Opiate Action Team, "Ohio Guideline for the Management of Acute Pain Outside of Emergency Departments," 2016, available at

Ohio has particular requirements for prescribers before writing prescriptions for controlled substances for chronic pain, including conducting an individualized examination of the patient and evaluating the risks of the medicine.[63] While specifics of these guidelines may vary from state to state and change over time, in my practice, I require frequent urine drug screens, a screen for opioid use disorder, a review of medication history, and corroborating data (e.g., medical records, previous hospitalizations), with careful attention to discrepancies, as well as a review of the PDMP. There are also other assessments physicians can undertake. For example, in my assessment of opioid suitability, I perform examinations for track marks (puncture wounds resulting from intravenous drug abuse), other signs of substance abuse (pupil size, agitation, restlessness, withdrawal symptoms), and other signs of inconsistency (such as gaps in prescriptions, changes in their prescriptions without an explanation, sudden change in prescribers without a valid explanation, or incomplete medical records).

58. When determining which medicine to prescribe, I follow general prescribing guidelines and consider a myriad of factors. I invariably focus on understanding the patient's problem, addressing the therapeutic objective, selecting the appropriate medication(s),

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https://mha.ohio.gov/Portals/0/assets/Initiatives/GCOAT/Guidelines-Acute-Pain-20160119.pdf, accessed May 1, 2019; Massachusetts Medical Society, "Opioid Therapy and Physician Communication Guidelines," 2015, available at http://www.massmed.org/Advocacy/Key-Issues/Opioid-Abuse/Opioid-Therapy-and-Physician-Communication-Guidelines-(pdf)/, accessed May 1, 2019; Medical Board of California, "Guidelines for Prescribing Controlled Substances for Pain," 2014, available at http://www.mbc.ca.gov/licensees/prescribing/pain_guidelines.pdf, accessed May 1, 2019.

[63] Ohio Rev. Cod. Ann. 4731.052(C). I understand that an Ohio practitioner may prescribe a controlled substance to his or her patient only after review of the patient's record and "potential for abuse" (*id.* 4731.052(E)), only after "other medically reasonable treatments for relief of the patient's chronic pain have been offered or attempted without adequate or reasonable success" (*id.* 4731.052(D)(3)(a)), and only with a "plan of treatment" and "periodic assessment and documentation for indicators of possible addiction, drug abuse, or drug diversion" (*id.* 4731.052(D)(3)(d)).

and consider alternative, non-pharmacological therapies in the scenario when the chosen medication is ineffective.[64] Detailing by pharmaceutical companies can also be a useful source of information on medication, including results from clinical trials, approved indications for the medication, as well as potential side effects. Detailing can be useful in keeping physicians up-to-date on the latest available scientific information.

59. Plaintiffs' experts' assumption that all detailing is false is inaccurate and unreasonable.[65] In fact, I have been detailed by representatives for various pharmaceutical companies regarding opioid medications, and in my experience have not found the marketing of opioids to be misleading or deceptive in all circumstances, as assumed by Plaintiffs' experts. I have never solely relied on information provided by a sales representative in writing an opioid prescription. Before making a treatment decision, I would evaluate many sources of information and consider the risks, benefits, and alternatives. I believe that a responsible physician would do the same.

60. Taken together, it is simply not possible to determine why physicians wrote prescriptions for opioids, without an individualized inquiry accounting for patient-specific

[64] Pollock, Madelyn, Oralia V. Bazaldua, and Alison E. Dobbie, "Appropriate prescribing of medications: an eight-step approach," *American Family Physician* Vol. 75, No. 2 (2007): 231-36, p. 1. *See also*, Munzing, Timothy, "Physician guide to appropriate opioid prescribing for noncancer pain," *The Permanente Journal* Vol. 21 (2017): 160-69. In 2016, the CDC developed the *CDC Guideline for Prescribing Opioids for Chronic Pain* to help physicians determine when to initiate opioid use for chronic pain, select appropriate opioid treatment, and assess the risks and harms of opioid use. *See*, Dowell, Deborah, Tamara M. Haegerich, and Roger Chou, "CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016," *Morbidity and Mortality Weekly Report* Vol. 65, No. 1 (2016): 1-49, p. 16.

[65] These assumptions occur, for example, in Expert Report of Matthew Perri III, *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019 ("Perri Report"), p. 138 ("I was asked to assume that the Plaintiffs' expert reports rendered in this case assessed the common messages delivered by the Defendants' marketing and hold the opinions that Defendants' messages were false, misleading, inaccurate, or designed to misstate the risks and benefits of Defendants' drugs."); Expert Report of Professor Meredith Rosenthal, *In Re National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019 ("Rosenthal Report"), p. 50 ("I have been instructed by counsel to assume in my but-for scenarios that the fact finder (judge or jury) finds that all or virtually all promotion by the manufacturer Defendants from 1995 to the present was unlawful.").

circumstances and the respective prescriber's considerations. When an opioid is prescribed, it is in the context of a physician-patient relationship and difficult to evaluate without consideration of the specific clinical circumstances.

VIII. OPINION #5: BEFORE WRITING A PRESCRIPTION OF ACTIQ OR FENTORA, PRESCRIBERS SHOULD CONSIDER THEIR RISKS. THEN THEY ARE REQUIRED TO REVIEW A MEDICATION GUIDE WITH PATIENTS, SIGN A PROVIDER-PATIENT AGREEMENT, AND COMPLY WITH THE OTHER REQUIREMENTS OF THE TIRF REMS PROGRAM.

61. Since their approval, Actiq and Fentora have been subject to Risk Mitigation programs because of the safety concerns associated with them. The FDA has exercised its authority to mandate a Risk Evaluation and Mitigation Strategy (REMS) for medications with serious safety concerns. Beginning in March 2012, the FDA included Actiq and Fentora in a class-wide REMS applicable to all TIRF medicines.

62. The FDA's TIRF REMS Program requires that prescribers, patients, and suppliers follow a set of procedures for prescribing and receiving TIRF medicines. By doing so, the FDA aims to achieve four objectives: (1) "prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients;"[66] (2) "preventing inappropriate conversion between TIRF medicines;"[67] (3) "preventing accidental exposure to children and others for whom it was not prescribed;"[68] and (4) "educating prescribers, pharmacists, and patients on the potential for misuse, abuse,

[66] TEVA_MDL_A_00709777-10056 at 00709810; TEVA_MDL_A_00710057-205 at 00710077.

[67] TEVA_MDL_A_00709777-10056 at 00709810; TEVA_MDL_A_00710057-205 at 00710077.

[68] TEVA_MDL_A_00709777-10056 at 00709810; TEVA_MDL_A_00710057-205 at 00710077.

addiction, and overdose of TIRF medicines."[69] I have been enrolled in the TIRF REMS Program since its inception.

63. In order to prescribe TIRF medicines like Actiq and Fentora in an outpatient setting, the TIRF REMS Program requires providers to review educational materials ("The Education Program") for each TIRF medicine, including the full prescribing information, and commit to the program requirements by signing a Prescriber Enrollment Form.[70] The Education Program provides guidance on a variety of important subjects, including identifying appropriate patients, contraindications, dosing, and specific thresholds of opioid tolerance.[71] Moreover, it contains information on risk factors for abuse and advises that "[a]ll patients treated with opioids require careful monitoring for sign of abuse and addiction."[72] Prescribers must successfully complete a knowledge assessment testing their understanding of The Education Program before enrolling in the TIRF REMS Program.[73] Prescribers must renew this enrollment every two years.[74]

[69] TEVA_MDL_A_00709777-10056 at 00709810; TEVA_MDL_A_00710057-205 at 00710077.

[70] FDA, "Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS)," August 2017, available at https://www.accessdata.fda.gov/drugsatfda_docs/rems/TIRF_2017-09-07_Full.pdf. For the latest FDA view on the REMS program, see, e.g. FDA, "REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary, Guidance for Industry," April 2019, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM521504.pdf.

[71] TIRF REMS Access, "Education Program for Prescribers and Pharmacists," available at https://www.tirfremsaccess.com/TirfUI/rems/pdf/education-and-ka.pdf.

[72] TIRF REMS Access, "Education Program for Prescribers and Pharmacists," p. 4.

[73] TIRF REMS Access, "Education Program for Prescribers and Pharmacists," p. 2.

[74] TIRF REMS Access, "Prescriber Enrollment Form," available at https://www.tirfremsaccess.com/TirfUI/rems/pdf/prescriber-enrollment-form.pdf.

64. At the time of prescribing, the TIRF REMS Program further mandates that prescribers review one-on-one with their patients the therapeutic risks and benefits as well as safe storage and disposal of TIRF medications.[75] Both prescriber and patient must sign a TIRF REMS Patient-Prescriber Agreement Form ("Patient Form") indicating that such a review has taken place and certifying that "[the prescriber] has counseled [the] patient or their caregiver about the risks, benefits, and appropriate uses of the TIRF medicine."[76] The prescriber must also attest that "[a]t all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse."[77] Lastly, the prescriber must provide a copy of the form to the patient, retain one for his or her records, and submit one to the TIRF REMS Program within 10 days of writing the prescription.[78]

65. As noted in the FDA's goals, these stringent requirements are meant to ensure that prescribers and patients are fully informed of the risks and approved indications of TIRF medications like Actiq or Fentora. The clear mandates and certifications of the TIRF REMS Program, including having to acknowledge the risks and approved indications of those medicines, show that a prescriber could not be misled into writing an inappropriate prescription for Actiq or Fentora.

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[75] TIRF REMS Access, "An Overview for Prescribers," available at https://www.tirfremsaccess.com/TirfUI/rems/pdf/prescriber-overview.pdf ("Step 2: Counsel Patients. Counsel the patient about the benefits and risks of TIRF medicines and together review the appropriate product-specific Medication Guide.").

[76] TIRF REMS Access, Patient-Prescriber Agreement Form, available at https://www.tirfremsaccess.com/TirfUI/rems/pdf/ppaf-form.pdf.

[77] FDA, "Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS)," p. 3.

[78] FDA, "Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS)," p. 3.

IX. OPINION #6: MARKETING MATERIALS AND SPONSORED RESEARCH CAN BE USEFUL SOURCES OF INFORMATION FOR PHYSICIANS, AND THE ACTIQ AND FENTORA MARKETING MATERIALS I REVIEWED ARE CONSISTENT WITH THEIR RESPECTIVE LABELS AND ARE NOT FALSE OR MISLEADING.

66. Pharmaceutical companies' marketing materials can be a useful source of information about new treatments, new uses for existing treatments, and corresponding risks and benefits. I have seen many marketing materials from pharmaceutical companies in my practice. In my experience, physicians approach such materials with skepticism, paying special attention to safety information, knowing that representatives of pharmaceutical companies have an incentive to sell their product.[79] With this critical perspective, some marketing materials, including detailing to physicians, can be informative and valuable for physicians. It is certainly not true that all marketing (or detailing) is inherently misleading or deceptive, as Plaintiffs' experts assume.[80]

A. Generic Medicines Are Generally Not Promoted To Physicians.

67. It is my understanding that pharmaceutical companies typically do not promote generic products.[81] Indeed, I have never been detailed by a sales representative with respect to a generic medicine. This is also consistent with the testimony of Plaintiffs' experts, who

[79] Kesselheim, Aaron S. et al., "A Randomized Study of How Physicians Interpret Research Funding Disclosures," *New England Journal of Medicine* Vol. 367, No. 12 (2012): 1119-27; Lacasse, Jeffrey R and Jonathan Leo, "Knowledge of ghostwriting and financial conflicts-of-interest reduces the perceived credibility of biomedical research," *BMC Research Notes* Vol. 4, No. 27 (2011): 1-6

[80] Rosenthal Report, p. 50 ("I have been instructed by counsel to assume in my but-for scenarios that the fact finder (judge or jury) finds that all or virtually all promotion by the manufacturer Defendants from 1995 to the present was unlawful.").

[81] On the differences between generic and branded pharmaceutical products, see FDA, "Generic Drugs: Questions & Answer," available at https://www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm100100.htm, accessed March 18, 2019.

have confirmed that the business model for generic medicines is different than the business model for brand-name medications, in that generic manufacturers generally do not promote their generic medicines to physicians.[82] Dr. Rosenthal, for instance, made this point clear: "Generally, manufacturers will not detail physicians for generics. They may have other sales force activities that they do that relate to price, but individual physicians are not generally making a decision about one generic versus the other. That decision happens at the pharmacy."[83]

68. As I understand it, that principle applies to the generic opioid medications of Teva USA and the Actavis Generic Defendants. For instance, Christine Baeder, the head of Teva USA's generic segment, testified that Teva USA does not promote generic medications to physicians because "[t]he decision-maker in generic procurement is not the physician. It's the officer at a corporate retail chain."[84] Likewise, Michael Perfetto, former Vice President of Actavis Sales and Marketing, testified that "we use quality, product supply, and pricing primarily to sell our [generic] products."[85] Andy Boyer, former Senior Vice President of Actavis Sales and Marketing and a former executive for Teva USA, added

[82] Deposition of Matthew Perri III, *In Re: National Prescription Opiate Litigation* MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, April 24, 2019 ("Deposition of Matthew Perri III"), p. 554 ("It's just simply that when we look at the overall balance for generics, we generally aren't going to see a lot of personal selling and we're not going to see a lot of personal selling related to the risks or possible harms of opioids. It's just an artifact of the market. Again, it's not judgmental, it's just this is the state of where we are, this is what's typically done in that marketing.").

[83] Deposition of Meredith Rosenthal, *In Re: National Prescription Opiate Litigation* MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, May 4, 2019 ("Deposition of Meredith Rosenthal"), pp. 197-198.

[84] Deposition of Christine Baeder, *In Re: National Prescription Opiate Litigation* MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, January 24, 2019 ("Deposition of Christine Baeder"), p. 416:5–15.

[85] Deposition of Michael Perfetto, *In Re: National Prescription Opiate Litigation* MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, December 18, 2018 ("Deposition of Michael Perfetto"), p. 315:24–316:2.

that "[i]t is physically impossible for a generic[s] company to hire enough sales representatives to go in and speak to physicians about all of [their] generic[s] products."[86] Mr. Boyer also noted that, "We don't detail products . . . [t]hese are not brands, these are generics. We offer up a price and we offer up a consistent supply in our supply chain and hopefully quality products . . . There's no pushing, there's no detailing, there's nothing else there."[87]

B. The Actiq and Fentora Marketing Materials I Reviewed are Consistent with their Respective Labels and Would Not Have Caused a Provider to Write a Prescription That Was Medically Inappropriate or Unnecessary.

69. I have reviewed hundreds of Actiq and Fentora marketing documents and I find these documents to be consistent with the label. All of the documents I reviewed contain clear descriptions of the approved indications, safety information, and risk of abuse.[88] In fact, many of the marketing materials I reviewed include the FDA-approved label for Actiq and Fentora and discuss the requirements of the TIRF REMS Program.[89] For example, one journal ad for Actiq includes a black box warning, and prescribing information with

[86] Deposition of Andrew Boyer, *In Re: National Prescription Opiate Litigation* MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, January 15, 2019 ("Deposition of Andrew Boyer"), p. 317:3–7.

[87] Deposition of Andrew Boyer, p. 346:9–17.

[88] "Actiq Marketing Materials," TEVA_MDL_A_00695218-6810; "Fentora Marketing Materials," TEVA_MDL_A_00025238-33471.

[89] See, e.g. TEVA_MDL_A_00695218-6810, at 00695600; TEVA_MDL_A_00025238-33471, at 00028116–00028124.

greater detail on adjacent pages.[90] Another, a table top panel for Fentora, has similar information and warnings, including the approved indication.[91]

70. Based upon my experience as a trained physician, I do not find the materials I reviewed to be false or misleading, and, in my opinion, they would not cause a prescriber to write an opioid prescription that was medically inappropriate or unnecessary. Indeed, Plaintiffs' expert, Dr. Lembke, identifies allegedly misleading promotional messages from several Defendants, but notably does not identify any from the Teva Defendants.[92] Neither does Dr. Schumacher, another one of Plaintiffs' experts.[93]

C. Receiving Support from Pharmaceutical Companies Does Not Necessarily Invalidate Third-Party Research, and the Third-Party Publications That Plaintiffs Seek to Attribute to the Teva Defendants That I Reviewed Were Not False or Misleading.

71. A number of Plaintiffs' experts reject published company-sponsored research that lends support to the suitability of opioid treatment in certain contexts. For instance, Dr. Perri asserts that "the credibility of the information in [a] publication is diminished" when "commercial interests are not disclosed."[94]

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[90] TEVA_MDL_A_00695218-6810, at 00695600.

[91] TEVA_MDL_A_00025238-33471, at 00028116–00028124.

[92] Lembke Report, Appendix I. I understand that in 2008, Cephalon paid restitution for violations of the False Claims Act for practices undertaken prior to October 2001, as discussed by Dr. Kessler in his report. As discussed in Section IX.B, the more recent Actiq and Fentora marketing materials I reviewed did not appear to be misleading or deceptive. Expert Report of David Kessler, M.D., *In Re National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019 ("Kessler Report"), pp. 200-224.

[93] Deposition of Mark A. Schumacher, M.D., Ph.D., *In Re: National Prescription Opiate Litigation* MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, April 23, 2019 ("Deposition of Mark A. Schumacher, M.D., Ph.D."), pp. 102-105 (testifying that he could not identify any false statements by the Teva or Actavis Generic Defendants and "do[es] not have evidence" for those companies).

[94] Perri Report, p. 36.

72. Based upon my experience as a trained physician, the third-party studies and publications regarding opioids that Plaintiffs and their experts seek to attribute to Cephalon or Teva USA are not false or misleading, and, in my opinion, would not mislead a physician into writing a medically inappropriate or unnecessary opioid prescription.[95]

[95] These studies are: American Pain Foundation, Treatment Options: A Guide for People Living with Pain; Bennett, Daniel S., "Breakthrough Pain: Treatment Rationale With Opioids," https://www.medscape.org/viewarticle/461612, accessed April 11, 2018; Brennan, Michael J., Steven D. Passik, and Kenneth L. Kirsh, "Pharmacologic Management of Breakthrough or Incident Pain," 2003, available at https://www.medscape.org/viewarticle/449803_print, accessed April 11, 2019; Cephalon, Inc., *Opioid Medications and REMS: A Patient's Guide*, 2010; Cephalon, Inc., *Special Report: An Integrated Risk Evaluation and Mitigation Strategy for Fentanyl Buccal Tablet (Fentora) and Oral Transmucosal Fentanyl Citrate (Actiq)*, 2011; Chou et al., "Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain," *The Journal of Pain* Vol. 10, No. 2 (2009): 113-30. e22; FDA, "A Guide to Safe Use of Pain Medicine," available at https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm095673.htm, accessed April 4, 2019; Mercadante, Sebastiano et al., "Factors influencing the use of opioids for breakthrough cancer pain: A secondary analysis of the IOPS-MS study," *European Journal of Pain* Vol. 23, No. 4 (2018): 719-26; Fine, Perry G., Christine Miaskowski, and Michael Brennan, *SELECT (Stratify, Examine, Listen, Evaluate, Control, Tailor): Opioid-Based Management of Persistent and Breakhrough Pain*, 2008; Fine et al., "Long-term safety and tolerability of fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic pain: an 18-month study," *Journal of Pain and Symptom Management* Vol. 40, No. 5 (2010): 747-60; Fishman, Scott M., *Responsible Opioid Prescribing: A Physician's Guide* (Washington, DC: Waterford Life Sciences, 2007); Nalamachu, Srinivas et al., *Prescription Pain Medication: Preserving Patient Access While Curbing Abuse*, 2013; Passik, Steven D. et al., "Aberrant Drug-Related Behavior Observed During Clinical Studies Involving Patients Taking Chronic Opioid Therapy for Persistent Pain and Fentanyl Buccal Tablet for Breakthrough Pain," *Journal of Pain and Symptom Management* Vol. 41, No. 1 (2011): 116-25; Portenoy et al., "Prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain," *The Journal of Pain* Vol. 7, No. 8 (2006): 583-91; Slatkin, "Breakthrough Pain: Improving Recognition and Management to Enhance Quality of Life"; Substance Abuse and Mental Health Services Administration (SAMHSA), "The CBHSQ Report: How People Obtain the Prescription Pain Relievers they Misuse," 2017, available at https://www.samhsa.gov/data/sites/default/files/report_2686/ShortReport-2686.html, accessed March 6, 2019; Taylor et al., "Impact of breakthrough pain on quality of life in patients with chronic, noncancer pain: Patient perceptions and effect of treatment with oral transmucosal fentanyl citrate (OTFC®, ACTIQ®)," *Pain Medicine* Vol. 8, No. 3 (2007): 281-88; Vowles, Kevin E et al., "Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis," *Pain* Vol. 156, No. 4 (2015): 569-76; Webster, "Optimizing Opioid Treatment for Breakthrough Pain"; Webster et al., "Fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic cancer and noncancer pain: a randomized, double-blind, crossover study followed by a 12-week open-label phase to evaluate patient outcomes," *Pain Medicine* Vol. 14, No. 9 (2013): 1332-45; Webster et al., "Fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic cancer and noncancer pain: a randomized, double-blind, crossover study followed by a 12-week open-label phase to evaluate patient outcomes," *Pain Medicine* Vol. 14, No. 9 (2013): 1332-45.

73. For one, the articles and guidelines themselves warn against overly broad conclusions. As an example, in reporting the effects of opioid therapy for CNCP, Portenoy and Foley advise readers that "[t]he conclusions of these studies must be interpreted cautiously in light of the ambiguities inherent in their data," and highlight the need for "[l]ong-term prospective studies of pain patients [... to] better assess the efficacy and risks of the treatment itself."[96] In my experience, this sort of cautious language is common in pain research, and physicians know that these sort of caveats matter.

74. In Dr. Scott Fishman's *Responsible Opioid Prescribing* – a book that Plaintiffs' experts identify as having received funding from the pharmaceutical industry, a fact it acknowledges at the start[97] – the author concludes that "[t]hese principles are presented as a basic framework for an organized, systematic practice. They offer substantial latitude and flexibility, allowing practitioners to deviate from these steps if, in their reasoned judgment, it's in the best medical interest of the patient. [...] Opioid analgesics are legitimate and effective agents for pain control. Nonetheless, they are not always indicated or appropriate. As always, clinicians must base their decisions to use or withhold opioids on a case-by-case risk/benefit analysis."[98]

[96] Portenoy, Russell K and Kathy M Foley, "Chronic Use of Opioid Analgesics in Non-Malignant Pain: Report of 38 Cases," *Pain* Vol. 25 (1986): 171-86, pp. 181, 184.

[97] Fishman, *Responsible Opioid Prescribing: A Physician's Guide* (2007), p. i ("This book is sponsored by a consortium of organizations with a common interest in promoting safe and effective pain management, including: [...] Cephalon, Inc.").

[98] Fishman, *Responsible Opioid Prescribing: A Physician's Guide* (2007), pp. 101-102.

75. Dr. Perry G. Fine et al.'s study of the long-term safety for fentanyl buccal tablets like Fentora, similarly, both acknowledges funding from Cephalon at the start and limits its findings.[99]

76. Further, the guidelines and papers that Plaintiffs' experts critique generally include clear acknowledgments of funding sources, and, in my experience, physicians know that checking for potential conflicts of interest is a key step in critically assessing new information. For example, the American Pain Society's 2009 "Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain" includes a multi-page appendix listing contributors' potential conflicts of interest.[100] Likewise, an article by Dr. Kenneth Portenoy et al., "Prevalence and Characteristics of Breakthrough Pain in Opioid-Treated Patients with Chronic Noncancer Pain," discloses Cephalon funding on its first page.[101] Such funding does not invalidate research findings, and when openly

[99] Fine et al., "Long-term safety and tolerability of fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic pain: an 18-month study," *Journal of Pain and Symptom Management* Vol. 40, No. 5 (2010): 747-60, p. 747 ("The study was sponsored by Cephalon, Inc. At the request of the authors, writing support was provided by David Peters of Sequoia Medical Communications, Ltd., funded by Cephalon, Inc. Dr. Fine has served as an advisory board member and consultant for Cephalon, Inc. Dr. Rathmell has served as a medical advisory board member for Cephalon, Inc. Drs. Messina and Xie are employees of Cephalon, Inc."), p. 758 ("There are few similar studies with which we can compare and contrast the safety and tolerability results of our investigation and none that specifically evaluates the long-term safety and tolerability of a potent opioid in the management of BTP in association with chronic noncancer pain. [...] The overall completion rate for this study was low (139 of 646; 22%). [...] Although the applicability of these findings to clinical practice is limited by the controlled nature of the clinical study setting, the study inclusion and exclusion criteria may offer an example of risk assessment and stratification standards that can identify patients for whom a trial of therapy with FBT might be most appropriate.")

[100] Chou et al., "Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain," *The Journal of Pain* Vol. 10, No. 2 (2009): 113-30.e22, pp. 130.e1-e4.

[101] Portenoy et al., "Prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain," *The Journal of Pain* Vol. 7, No. 8 (2006): 583-91, p. 583 ("Supported by a grant from Cephalon, Inc., West Chester, Pa. Cephalon has provided an unrestricted grant to Dr. Portenoy's department, and he has recently become a consultant to the company; he was not a paid consultant at the time that this study was conducted. Drs. Simon, Brennan, Taylor, and Shoemaker are consultants to Cephalon and are on the Speaker's Bureau for Cephalon.").

acknowledged, readers can assess for themselves how much to rely upon each piece of evidence.

77. Critically assessing scientific studies, clinical guidelines, and other sources of information is a key part of the practice of medicine. In my experience, physicians understand that no single study is definitive. Manufacturer funding and various limitations, including small sample sizes, are common in scientific studies, yet peer-reviewed research adds valuable contributions nonetheless. These studies, and other studies that the Plaintiffs' experts critique, contain useful information for physicians in pain management, even if they (like all science) are produced by human beings, are inevitably imperfect, and should be weighed against all other information at a physician's disposal.

X. OPINION #7: ADDICTION IS A RISK NOT ONLY OF OPIOIDS BUT ALSO OF NUMEROUS MEDICATIONS AND IS THE RESULT OF MANY FACTORS. MOREOVER, PHYSICIANS HAVE LONG KNOWN OF THE ADDICTION RISKS ASSOCIATED WITH OPIOID MEDICINES LIKE ACTIQ AND FENTORA.

78. Addiction is "a primary, chronic, disease of brain reward, motivation, memory and related circuitry," influenced by psychosocial, genetic, and environmental factors.[102] The link between opiate addiction and neurobiologic processes has long been understood. In short, ingesting opiates, as well as other major substances of abuse like alcohol, increase levels of the neurotransmitter dopamine in the brain, which may result in a number of

[102] American Society of Addiction Medicine, "Definition of Addiction," 2011, available at https://www.asam.org/resources/definition-of-addiction, accessed May 9, 2019.

symptoms, including powerful feelings of pleasure.[103] If subjected to artificially high levels of dopamine consistently, the brain will reduce its internal supply of the neurotransmitter in an attempt to maintain homeostasis.[104] Thus, limiting or halting opioid ingestion after consistent use may result in low dopamine levels and other neurotransmitter imbalances, with symptoms including but not limited to depression, anxiety, panic attacks, and insomnia.[105] The drive to avoid or alleviate such symptoms can lead to further opiate ingestion and a resulting cycle of dependence.[106] Furthermore, abrupt cessation of opioids can lead to opioid withdrawal syndrome, which includes drug craving, agitation, anxiety, insomnia, runny nose, goosebumps, sweating, abdominal cramps, diarrhea, and vomiting.[107] While dopamine levels drop, norepinephrine levels increase and are responsible for many of the symptoms of opioid withdrawal.[108]

79. It is important to note many substances carry this potential for addiction. Substance-related epidemics and public health crises have been and remain all too common. For one, according to the CDC, "alcohol abuse contributes to 88,000 deaths in the United States each year," a figure that represents twice the annual deaths associated with opioid

[103] Kosten, Thomas R and Tony P George, "The neurobiology of opioid dependence: implications for treatment," *Science & Practice Perspectives* Vol. 1, No. 1 (2002): 13-20, p. 14.

[104] American Addiction Centers, "Drug Abuse and Chemical Imbalance in the Brain: Dopamine, Seratonin & More," available at https://americanaddictioncenters.org/health-complications-addiction/chemical-imbalance, accessed April 26, 2019.

[105] American Addiction Centers, "Drug Abuse and Chemical Imbalance in the Brain: Dopamine, Seratonin & More."

[106] American Addiction Centers, "Drug Abuse and Chemical Imbalance in the Brain: Dopamine, Seratonin & More."

[107] Medline Plus, "Opiate and Opioid Withdrawal," available at https://medlineplus.gov/ency/article/000949.htm, accessed April 23, 2019.

[108] Kosten and George, "The neurobiology of opioid dependence: implications for treatment," *Science & Practice Perspectives* Vol. 1, No. 1 (2002): 13-20.

abuse.[109] Moreover, at various points over the previous century, widespread abuse of other narcotics, such as cocaine and methamphetamine, have captured the nation's attention and necessitated public and private action.[110]

80. Given this history, it should not be surprising that the link between opioid-intake and an increased risk of physical dependence and/or addiction has been well understood for decades. Since at least the early 1990s, the scientific literature on opioid treatment has been consistent in acknowledging the potential for addiction as "a major issue in the use of opioid drugs for the management of chronic [malignant and] nonmalignant pain."[111] Indeed, well before concerns over opioid abuse reached the public's consciousness, the medical and scientific community had developed a large body of research on the subject. By the early-2000s, studies on the efficacy of opioids for chronic and acute pain relief and the possible under-treatment of pain due to concern over the risk of opioid abuse had become commonplace.[112] Since at least the mid-2000s, there has been significant

[109] Centers for Disease Control and Prevention, "Fact Sheets - Alcohol Use and Your Health," available at https://www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm, accessed March 8, 2019 ("Excessive alcohol use led to approximately 88,000 deaths and 2.5 million years of potential life lost (YPLL) each year in the United States from 2006 – 2010, shortening the lives of those who died by an average of 30 years."); National Institute on Drug Abuse, "Overdose Death Rates," January 2019, available at https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates, accessed March 8, 2019.

[110] Frakt, Austin, "Overshadowed by the Opioid Crisis: A Comeback by Cocaine," *The New York Times* March 5, 2018; Robles, Frances, "Meth, the Forgotten Killer, Is Back. And It's Everywhere," *The New York Times* February 13, 2018; Stobbe, Mike, "Today's Opioid Crisis Shares Chilling Similarities with Past Drug Epidemics," *The Chicago Tribune* October 28, 2017.

[111] Portenoy, Russell K, "Opioid therapy for chronic nonmalignant pain: clinicians' perspective," *The Journal of Law, Medicine & Ethics* Vol. 24, No. 4 (1996): 296-309, p. 5.

[112] Rosenblum, Andrew et al., "Opioids and the treatment of chronic pain: controversies, current status, and future directions," *Experimental and Clinical Psychopharmacology* Vol. 16, No. 5 (2008): 405-16, p. 405 ("Historically, concerns about addiction have apparently contributed to the under-treatment of disorders widely considered to be appropriate for opioid therapy, including cancer pain, pain at the end-of-life, and acute pain.").

research on the appropriateness of opioid treatment for non-cancer pain and the risk of addiction, in general.[113]

81. The FDA labels for Actiq and Fentora reflect this heightened scrutiny of the relationship between opioid treatment and the potential for addiction. As noted above, the FDA labels for Actiq and Fentora contain numerous warnings and precautions centered on the risk of abuse.[114] Both Actiq and Fentora labels contain black-box warnings that state, "[ACTIQ or FENTORA] exposes users to risk of addiction, abuse, and misuse, which can lead to overdose and death" and directives to physicians to "[a]ssess patient's risk before prescribing and monitor closely for these behaviors and conditions."[115] Similar language is repeated throughout both labels.[116] Moreover, the fact that both labels note clearly that these medications should only be dispensed to opioid tolerant outpatients enrolled in the

[113] Vowles et al., "Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis," *Pain* Vol. 156, No. 4 (2015): 569-76; Fishbain, David A et al., "What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review," *Pain Medicine* Vol. 9, No. 4 (2008): 444-59; Ballantyne, Jane C, "Opioids for the treatment of chronic pain: mistakes made, lessons learned, and future directions," *Anesthesia & Analgesia* Vol. 125, No. 5 (2017): 1769-78; Volkow, Nora D and A Thomas McLellan, "Opioid abuse in chronic pain—misconceptions and mitigation strategies," *New England Journal of Medicine* Vol. 374, No. 13 (2016): 1253-63; Højsted, Jette and Per Sjøgren, "Addiction to opioids in chronic pain patients: a literature review," *European Journal of Pain* Vol. 11, No. 5 (2007): 490-518.

[114] "Actiq Label, December 2016"; "Fentora Label, April 2017." While overall societal scrutiny of opioid addiction has heighted, the original labels were also clear about these kinds of risks. TEVA_MDL_A_00709777-10056, at 00709785 (e.g., "Actiq contains fentanyl, […] with an abuse liability similar to other opioid analgesics. Actiq can be abused in a manner similar to other opioid agonists, legal or illicit."); Fentora 2006 ("FENTORA contains [...] a Schedule II controlled substance with high potential for abuse similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Fentanyl can be abused and is subject to misuse, and criminal diversion. [...] [A]ll patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use").

[115] "Actiq Label, December 2016"; "Fentora Label, April 2017."

[116] "Actiq Label, December 2016"; "Fentora Label, April 2017."

TIRF REMS Access Program dispels any notion that physicians lack information on these medications' potential for abuse and/or misuse.

82. However, it is important to avoid confusing addiction with physical dependence. Whereas physiological dependence involves the presence of tolerance and withdrawal symptoms, addiction, as noted above, is a primary, chronic, neurobiologic disease, whose development and manifestations are influenced by genetic, psychosocial, and environmental factors.[117] Physiological dependence "can occur even at prescribed doses in non-addicted individuals."[118]

83. A brief overview of the DSM-V's definition of "opioid use disorder" is instructive for understanding this important distinction. In order for an individual to meet the diagnostic criteria for "opioid use disorder," he or she must exhibit "a problematic pattern of opioid use leading to a clinically significant impairment or distress," defined as exhibiting at least two of eleven symptoms ranging from "persistent desire or unsuccessful efforts to cut down or control opioid use" to "craving, or a strong desire or urge to use opioids" to "tolerance"[119] to "withdrawal."[120] Critically, however, the DSM-V notes that the criterion for "tolerance" and "withdrawal" "is not considered to be met for those taking opioids solely under appropriate medical supervision."[121] This important caveat recognizes that

[117] American Society of Addiction Medicine, "Definitions Related to the Use of Opioids for the Treatment of Pain: Consensus Statement of the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine."

[118] Ling, Walter, Larissa Mooney, and Maureen Hillhouse, "Prescription opioid abuse, pain and addiction: clinical issues and implications," *Drug and Alcohol Review* Vol. 30, No. 3 (2011): 300-05.

[119] American Psychiatric Association, "Opioid Use Disorder," *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V)* (2013).

[120] American Psychiatric Association, "Opioid Use Disorder."

[121] American Psychiatric Association, "Opioid Use Disorder."

while patients may often develop physical withdrawal symptoms and tolerance to prescribed opioids, these are, in and of themselves, not sufficient for a "disorder" diagnosis. In other words, the DSM-V makes clear that a patient's development of physical dependence during treatment of serious pain is not sufficient for an addiction classification.

84. In short, CNCP patients with opioid-dependence stemming from clinically supervised treatment often continue to benefit from opioid treatment. In my own clinical experience, opioids can play a significant role in the management of CNCP. If a patient develops signs of OUD and/or addiction, then their treatment plan is re-evaluated and revised. Opioid taper, opioid rotation, abrupt opioid withdrawal, initiation of Medication-Assisted Treatment (MAT) with buprenorphine, and referral for inpatient treatment are some of the possible next steps.

85. Further, to predict opioid abuse based only on whether or not a patient is on opioid therapy contradicts basic addiction science. The medical community has long understood that a plethora of variables contribute to addiction, and opioid addiction specifically. For example, patients with untreated depression and other mental health disorders are at increased risk for misuse, abuse, and/or addiction in connection with controlled medications.[122] Other environmental forces like childhood trauma, prevalent substance abuse in one's household and/or social circle, and excessive stress can also predispose one to addiction. In addition, there may be genetic underpinnings of an individual's

[122] Federation of State Medical Boards, "Guidelines for the Chronic Use of Opioid Analgesics," April 2017, available at http://www.fsmb.org/siteassets/advocacy/policies/opioid_guidelines_as_adopted_april-2017_final.pdf.

predisposition to substance abuse. Though scientific understanding of addiction-producing genome elements remains limited, studies have demonstrated a strong link between genetic background and addictive disorders.[123]

86. The complex dynamics behind patients' risk of addiction highlight the importance of individualized treatment rather than a one-size-fits-all approach in prescribing opioids for CNCP. Physicians should not withhold a potential solution to debilitating pain from a patient who does not exhibit risks of abuse simply because a relationship exists between that solution and addiction. Such under-treatment of pain not only reveals a misunderstanding of addiction but also can have devastating effects on patient quality-of-life and physical well-being.[124]

87. Since the CDC issued guidelines in 2016 for the prescription of opioids, physicians have become increasingly fearful of prescribing opioids.[125] This has led to tragic outcomes including forced taper, under-treatment of chronic pain, and suicide.[126] In response to these unintended consequences for patients, the authors of the 2016 CDC guidelines issued a statement in April 2019 cautioning against misapplication of the guidelines and

[123] Mistry, Chetna J. et al., "Genetics of opioid dependence: a review of the genetic contribution to opioid dependence," *Current Psychiatry Reviews* Vol. 10, No. 2 (2014): 156-67; Berrettini, Wade, "A brief review of the genetics and pharmacogenetics of opioid use disorders," *Dialogues in Clinical Neuroscience* Vol. 19, No. 3 (2017): 229-36.

[124] Rosenberg, Mark, "Undertreated Pain Epidemic: Multi-Modality Approach to Pain Management," *Journal of Managed Care Medicine* Vol. 15, No. 1 (2012): 30-37.

[125] Dowell, Deborah, Tamara Haegerich, and Roger Chou, "No Shortcuts to Safer Opioid Prescribing," *New England Journal of Medicine* (2019): Online at https://www.nejm.org/doi/full/10.1056/NEJMp1904190.

[126] Heubusch, John, "The War on Opioids is Saving Lives. But It's Also Killing People Like Me.," *The Washington Post*, March 27, 2019, available at https://www.washingtonpost.com/opinions/the-war-on-opioids-is-saving-lives-but-its-also-killing-people-like-me/2019/03/27/cea00af6-50c2-11e9-a3f7-78b7525a8d5f_story.html, accessed April 26, 2019; Sullum, Jacob, "America's War on Pain Pills Is Killing Addicts and Leaving Patients in Agony," March 8, 2018, available at https://reason.com/2018/03/08/americas-war-on-pain-pills-is/, accessed April 26, 2019.

physicians adhering too strictly to their interpretation of the guidelines, which deprived patients of needed care.[127] An article that explains the update states: "Unfortunately, some policies and practices purportedly derived from the [2016] guideline have in fact been inconsistent with, and often go beyond, its recommendations… Such actions are likely to result in harm to patients."[128] These harmful actions include inflexible application of recommended dosage, abrupt opioid discontinuation, and discharge of patients from a physician's practice.[129] A 2019 clarification by the authors of these CDC guidelines advocates for individual assessment of each patient's needs.[130] It is important to treat each case individually to provide the best outcome for each patient.

XI. OPINION #8: SOME PATIENTS ON OPIOID THERAPY EXPERIENCE THE NEED FOR MORE PAIN RELIEF WITHOUT BEING ADDICTED TO OPIOIDS.

88. In my clinical experience, I have treated many patients on opioid therapy who experience the need for more pain relief, and therefore exhibit behaviors that can be mistaken for drug-seeking behavior, yet who are not addicted. This can sometimes be linked to episodic breakthrough pain episodes disrupting patients' lives. Some practitioners refer to this phenomenon as "pseudoaddiction," a concept first recognized in 1989, well before

[127] Centers for Disease Control and Prevention, "CDC Advises Against Misapplication of the Guideline for Prescribing Opioids for Chronic Pain."

[128] Dowell et al., "No Shortcuts to Safer Opioid Prescribing," *New England Journal of Medicine* (2019): Online at https://www.nejm.org/doi/full/10.1056/NEJMp1904190.

[129] Dowell et al., "No Shortcuts to Safer Opioid Prescribing," *New England Journal of Medicine* (2019): Online at https://www.nejm.org/doi/full/10.1056/NEJMp1904190.

[130] Centers for Disease Control and Prevention, "CDC Advises Against Misapplication of the Guideline for Prescribing Opioids for Chronic Pain."

any Teva Defendant ever started to sell opioid medications.[131] Whatever term one uses, the pain these patients experience is real. It is reasonable to expect physicians who practice pain management to recognize addiction. Identifying addiction, however, is more complicated than using simple checklists, and physicians must address each case individually.

89. One particularly well-known incident centered on a 17-year-old man with acute leukemia who had been hospitalized for pneumonia and chest pain.[132] After days of receiving 5mg of intravenous morphine every four to six hours, the patient began to engage in common drug-seeking behaviors including requesting medication prior to scheduled dosing and "engag[ing] in progressively escalated pain behavior, such as vocalizations…grimacing, or holding affected body parts."[133] Following subsequent examination, however, physicians determined the patient had not been exhibiting addictive drug-seeking behavior but instead had been merely responding to under-treatment of his pain. In short, engaging in seemingly drug-seeking behaviors may reflect the patient's actual need for additional therapy, which requires the physician's additional attention.[134]

90. Many individuals may request more pain relief simply to satisfy their addiction; others may not be receiving adequate pain relief, whether or not they are addicted. To this day,

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[131] Weissman, David E and J David Haddox, "Opioid pseudoaddiction—an iatrogenic syndrome," *Pain* Vol. 36, No. 3 (1989): 363-66; Passik, Steven D, Kenneth L Kirsh, and Lynn Webster, "Pseudoaddiction revisited: a commentary on clinical and historical considerations," *Pain Management* Vol. 1, No. 3 (2011): 239-48.

[132] Weissman and Haddox, "Opioid pseudoaddiction—an iatrogenic syndrome," *Pain* Vol. 36, No. 3 (1989): 363-66; Passik et al., "Pseudoaddiction revisited: a commentary on clinical and historical considerations," *Pain Management* Vol. 1, No. 3 (2011): 239-48.

[133] Weissman and Haddox, "Opioid pseudoaddiction—an iatrogenic syndrome," *Pain* Vol. 36, No. 3 (1989): 363-66, p. 364.

[134] Weissman and Haddox, "Opioid pseudoaddiction—an iatrogenic syndrome," *Pain* Vol. 36, No. 3 (1989): 363-66, p. 364.

pain is still undertreated for many patients. For example, sickle cell patients with frequent hospitalizations for crisis become tolerant to administered IV opioids and will often require higher doses than other "opioid naïve" patients. Recent articles by chronic pain sufferers describe the "countless unsuccessful procedures and near superhuman efforts [needed] to be granted barely enough medication to try to live a normal life," as fears of overprescribing opioids lead to reactive underprescribing.[135] These "superhuman efforts" to acquire sufficient analgesia to live a normal life can often be misunderstood as "drug seeking."

91. The reality and consequences of undertreated pain accentuate why a physician must take an individualized approach to treating each patient.

XII. OPINION #9: PRESCRIPTION OPIOIDS, INCLUDING ACTIQ AND FENTORA, HAVE AN ACCEPTABLE AND MANAGEABLE RISK OF MISUSE, ABUSE, AND ADDICTION WHEN PRESCRIBED PROPERLY AND IN CONJUNCTION WITH THOROUGH SCREENING AND MONITORING.

92. Physicians can manage the well-known risks associated with opioid medications, including Actiq and Fentora, through the appropriate screening and monitoring of patients. For example, a physician considering prescribing opioids for CNCP must assess whether a patient has a history of substance abuse, since these patients are "significantly more likely to exhibit or report prescription medication misuse."[136] As detailed further in Opinion #4 above, the physician must assess the decision to prescribe opioids on a patient-by-patient basis after carefully assessing the risks and benefits.

[135] Heubusch, "The War on Opioids is Saving Lives. But It's Also Killing People Like Me."; Sullum, "America's War on Pain Pills Is Killing Addicts and Leaving Patients in Agony."

[136] Morasco, Benjamin J et al., "Systematic review of prevalence, correlates, and treatment outcomes for chronic non-cancer pain in patients with comorbid substance use disorder," *Pain* Vol. 152, No. 3 (2011): 488-97.

93. In the case of Actiq and Fentora, the earlier Risk Management Programs and the current TIRF REMS Program have helped inform both patients and physicians of the risks, benefits, appropriate use, indications, abuse, and overdose potential associated with these medications. In addition, the TIRF REMS Program requires screening for addiction potential and follow-up evaluations for misuse, abuse, and/or aberrant behavior.[137] Given that past addiction is a strong predictor of opioid misuse, the TIRF REMS Program centers on the physician's individualized assessment of a patient's needs and risk profile to provide education safeguarding against the risk of abuse.

94. As I describe in Opinion #4 above, there are many steps a physician can take to manage the risk of opioid abuse while treating CNCP with Actiq or Fentora. When treating patients for CNCP using opioids, I take many steps to manage this risk, such as reviewing medication history, requiring urine drug screens, and PDMP review. This is the standard of care that I would expect among principled pain management professionals with whom I interact.

XIII. OPINION #10: PEOPLE WHO MISUSE, ABUSE, OR BECOME ADDICTED TO PRESCRIPTION OPIOIDS OFTEN OBTAIN THEM WITHOUT A PRESCRIPTION.

95. In my experience, I have treated many patients who became addicted to prescription opioids without receiving a prescription for them. The 2013 and 2014 National Survey on Drug Use and Health shows that at least 70% of respondents who misused a prescription opioid in the past year turned to the secondary market for the prescription pain relievers

[137] FDA, "Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS)."

that they had most recently misused.[138] Research regarding opioid prescribing often notes the extent of diversion stemming from legal prescribing, with one study estimating that between 3.3 and 4.3 million lawful opioid prescriptions are diverted annually for illegal dealing.[139] The importance of this issue is also reflected in the CDC's opioid prescribing guidelines, which identify lowering rates of diversion as a key motivation for both limiting the supply days of opioid prescriptions and requiring urine testing prior to prescribing opioids.[140]

96. For example, I have treated thousands of patients in the acute care hospital setting who enter the medical system with a variety of presenting illnesses and, during the course of their hospitalization exhibit symptoms of opioid abuse, misuse, or addiction, without any record of a legitimate opioid prescription. These patients, therefore, had been acquiring opioids in other ways. In all, thousands of patients I have treated: (1) are taking more opioids than prescribed (a red flag for addiction); (2) are taking less than is prescribed (a red flag for diversion); or (3) claim to be prescribed prescription opioids, but do not have a legitimate prescription (another red flag). In addition, in my experience with these patients and based on broader research, many people who misuse, abuse, or become addicted to opioids take illegally made or "illicit" opioids that are not manufactured by

[138] Substance Abuse and Mental Health Services Administration (SAMHSA), "The CBHSQ Report: How People Obtain the Prescription Pain Relievers they Misuse." This 70.7% figure represents the following sources: "From a friend of relative for free" (50.5%), "Bought from friend or relative" (11%), "Took from friend or relative without asking" (4.4%), "Bought from drug dealer or other stranger" (4.8%). It does not include "Other" (4.1%).

[139] Simeone, Ronald, "Doctor Shopping Behavior and the Diversion of Prescription Opioids," *Substance Abuse: Research and Treatment* Vol. 11 (2017): 1-10.

[140] Dowell et al., "CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016," *Morbidity and Mortality Weekly Report* Vol. 65, No. 1 (2016): 1-49.

pharmaceutical companies.[141] Indeed, according to the CDC and the Department of Justice's Drug Enforcement Administration, "most recent cases of fentanyl-related harm, overdose, and death in the U.S. are linked to illegally made fentanyl."[142]

XIV. OPINION #11: OPIOID USE DISORDER CAN BE TREATED EFFECTIVELY THROUGH PHARMACOLOGIC AND NON-PHARMACOLOGIC METHODS.

97. As discussed above, with appropriate screening and ongoing monitoring of patients prescribed opioids, the risk of addiction can be significantly lowered to an acceptable and manageable level. However, this risk of addiction still exists for any opioid product (and indeed for many non-opioid prescription medications), regardless of the source.

98. In the event a patient presents with OUD, it is highly treatable. In my practice, I turn to both pharmacologic and non-pharmacologic methods for the effective treatment of OUD.

99. As with the treatment of pain, treatment of OUD should be tailored to each individual patient. Indeed, as explained in a recent Treatment Improvement Protocol (TIP) published by the U.S. Substance Abuse and Mental Health Services Administration (SAMHSA), "there is no 'one size fits all' approach to OUD treatment."[143] Medically supervised withdrawal, sometimes supplemented by medications such as clonidine or tizanidine to treat symptoms, can be a helpful first step.[144] Tapering off of opioids is

[141] Pergolizzi Jr, Joseph V et al., "Going beyond prescription pain relievers to understand the opioid epidemic: the role of illicit fentanyl, new psychoactive substances, and street heroin," *Postgraduate medicine* Vol. 130, No. 1 (2018): 1-8.

[142] Centers for Disease Control and Prevention, "Fentanyl," available at https://www.cdc.gov/drugoverdose/opioids/fentanyl.html, accessed March 18, 2019.

[143] Substance Abuse and Mental Health Services Administration (SAMHSA), "Treatment Improvement Protocol 63," https://www.ncbi.nlm.nih.gov/books/NBK535268/pdf/Bookshelf_NBK535268.pdf, p. ES-2.

[144] Schuckit, Marc A, "Treatment of opioid-use disorders," *New England Journal of Medicine* Vol. 375, No. 4 (2016): 357-68, p. 358-60.

another option, and in my experience is a more effective method than cutting off all opioids at once. Once the patient has recovered from the effects of physiological dependence, group and individual counseling using cognitive behavioral approaches can begin to address other dimensions of OUD.[145]

100. Some cases, such as treating OUD in pregnant women, require special care, and supervised withdrawal may not be appropriate.[146] In my own practice, I treat pregnant OUD patients with buprenorphine in order to reduce the risk of the mother using illicit substances, such as heroin, which is consistent with a harm reduction model.[147] One of the risks associated with opioid use during pregnancy, neonatal abstinence syndrome (NAS), can result from a pregnant woman taking any opioid drug, including heroin and other non-prescription opioids.[148]

XV. CONCLUSION

101. Plaintiffs in this case contend that all marketing for the opioid medications of the Teva and Actavis Generic Defendants, including Actiq and Fentora, in the Bellwether

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[145] Substance Abuse and Mental Health Services Administration (SAMHSA), "Treatment Improvement Protocol 63," available at https://www.ncbi.nlm.nih.gov/books/NBK535268/pdf/Bookshelf_NBK535268.pdf.

[146] World Health Organization, "Guidelines for the Identification and Management of Substance Use and Substance Use Disorders in Pregnancy," 2014, available at https://www.who.int/substance_abuse/publications/pregnancy_guidelines/en/; National Institute on Drug Abuse, "Treating Opioid Use Disorder during Pregnancy," 2017, available at https://www.drugabuse.gov/publications/treating-opioid-use-disorder-during-pregnancy/treating-opioid-use-disorder-during-pregnancy. These additional risks lead me to recommend even greater caution in prescribing opioids to pregnant women, though there may be individualized cases where this is an appropriate course of treatment.

[147] Bishop, Darla et al. *Pregnant Women and Substance Use: Overview of Research & Policy in the United States.* The George Washington University's Jacobs Institute of Women's Health (February 2017), pp. 24-25. Available at https://hsrc.himmelfarb.gwu.edu/sphhs_centers_jacobs/5/.

[148] "Neonatal Abstinence Syndrome," available at https://medlineplus.gov/ency/article/007313.htm, accessed May 5, 2019.

Jurisdictions was false and misleading.[149] However, this is contrary to my review of marketing materials that Plaintiffs attribute to the Teva Defendants, published research, and how prescribing decisions are made. It is also contrary to the principle that generic manufacturers, like Teva USA and the Actavis Generic Defendants, do not generally promote their opioid medications. It is also my understanding that Plaintiffs have not conducted a survey of any Ohio patients or prescribers to see whether they received or were influenced by any marketing by any of Teva Defendants. My opinion is that prescribers were well informed of the potential for misuse and abuse of Actiq and Fentora through product labeling, the components of these medicines, the Risk Management and TIRF REMS Programs, as well as through their education and training.

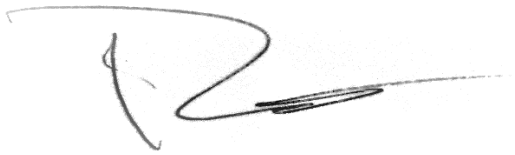
102. Both clinical research and my own experience as a practicing pain and addiction specialist demonstrate that opioids can be an effective treatment for CNCP with an acceptable and manageable risk of misuse, abuse, and addiction when prescribed properly and in conjunction with thorough screening and monitoring. Likewise, breakthrough pain is serious and debilitating for both cancer and non-cancer patients, and opioids, including Actiq and Fentora, can be an effective treatment for breakthrough pain. Ultimately, the decision to prescribe opioids, such as Actiq or Fentora, must be made by a physician on a case-by-case basis, considering the clinical history and risk factors for each patient. When

[149] Rosenthal Report, p. 50 ("I have been instructed by counsel to assume in my but-for scenarios that the fact finder (judge or jury) finds that all or virtually all promotion by the manufacturer Defendants from 1995 to the present was unlawful."); Perri Report, p. 138 ("I was asked to assume that the Plaintiffs' expert reports rendered in this case assessed the common messages delivered by the Defendants' marketing and hold the opinions that Defendants' messages were false, misleading, inaccurate, or designed to misstate the risks and benefits of Defendants' drugs.").

prescribing opioids, there is no one-size-fits-all approach to determining what is medically necessary or appropriate.

* * *

Signed on the 10th day of May, 2019.



Melanie H. Rosenblatt, M.D.

Appendix A

Curriculum Vitae

CURRICULUM VITAE

Melanie Rosenblatt, MD
1 West Sample Road, Suite 104
Pompano Beach, FL 33064
(954) 941-5556

Personal Data:

DOB: August 9, 1965
Place of birth: Brooklyn, NY

Education:

MD – State University of New York at Stony Brook
Stony Brook, NY
August 1987-May 1991

BS – State University of New York at Stony Brook
Stony Brook, NY
September 1983-December 1986

Hospital Training:

Residency- Anesthesiology- St. Joseph's Hospital Health Center
Syracuse, NY
July 1992- June 1995

Internship- Obstetrics and Gynecology- Nassau County Medical Center
East Meadow, NY
July 1991- June 1992

Practice/Employment History:

Pain Management Strategies, Inc.
1 West Sample Road, Suite #106
Pompano Beach, FL 33064
(954) 941-5556
April 2002- present

Pain Management Strategies, Inc. (2nd location)
Twin Lakes Professional Center
2900 N. Military Trail, Suite 241
Boca Raton, FL 33431
(561) 998-5100
June 2006- present

Medical Director of Pain Management
Broward Health North

July 2002- Oct 2017

Medical Director of Acute Pain Management
Holy Cross Hospital
Nov 2014- present
Imperial Point Medical Center
August 2014- present

Affiliate Faculty member of University of Miami
August 2016-present

Melrose Pain Solutions-Founding Partner
2016-present

Monitor for the Florida Board of Medicine
Probationers Committee
On-site visits to physician offices
July 2010- August 2012

Park Creek Surgical Center
6806 North State Road 7 (Route 441)
Coconut Creek, FL 33073
2007- 2012

Physicians Outpatient Surgery Center
1000 Northeast 56th St
Fort Lauderdale, FL 33334
2008- Present

Anesthesiologist for the North Broward Hospital District
APA/ANESCO
1995-2000

Director of Anesthesia
Atlantic Surgical Center
August 2002- September 2004

Clinical Instructor- Department of Surgery
Nova Southeastern University
College of Osteopathic Medicine
1997-2000

Committees:

C & Q chairperson
Broward Health North

2007-2016

Medical Executive Board Member
Broward Health North
2007- 2016

Publications:

Newsmax Health Weekly Blog (2 million viewers)
May 2015-present
Everyday Health- interview June 2014
Revolving Door of Opioid Addiction Jan 2017

Pain Medicine News
October 2016
Why CMS Should Not Remove Pain Questions From Payment Calculations
December 2016
DEA Ratchet's Down Opioid Production-Contributor

Future Medicine
November 2018
Tapering opioid therapy: clinical strategies
Joseph V Pergolizzi Jr, Melanie Rosenblatt, Dean J Mariano & John Bisney

Television/Film:

"Pain Matters"- the Discovery Channel Nov+ Dec 2015
Satellite Media Tour- San Francisco Sept 2014
Discovery Health Channel, Beacon TV April +May 2015

Appearances/Lectures:

CME lectures, multiple
Legislative Congress, Williamsburg PA June 2015
Legislative Congress, Sacramento CA Sept 2015
Legislative Congress, Salt Lake City UT Oct 2015
Complex Spine & Interventional Pain Symposium
Palm Beach, FL Nov 2017

Faculty Training/
Key Speaker:

Alpharma 2004-2006
KOL, Speaker/Speaker Training
National Sales Meeting, 2005

Medtronic 2005-2008
Trained surgeons on Intrathecal Baclofen implantation technique

St Jude Medical 2009-2013
Lectures, Cadaver Workshops, Round Tables
Peer-to-Peer Trainings

Collegium Conferences, Regional & National, multiple
Virtual WebEx, April 2016
Virtual WebEx, May 2016
Chicago IL June 2016
Orlando FL Aug 2016
Dallas TX Oct 2016
Virtual WebEx, Oct 2016
Orlando FL Oct 2016
Boca Raton FL Nov 2016
Palm Beach FL Nov 2016
Denver CO Dec 2016
Delray Beach FL Jan 2017

Pfizer Conferences, Regional & National, multiple
Pain Week, Los Vegas NV Sept 2016
Vero Beach FL Oct 2016
Palm Beach FL Nov 2016
West Palm FL Dec 2016

Depomed Conference, Regional & National, multiple
Ft Worth TX Mar 2017
West Palm FL Apr 2017
Tampa FL May 2017
Boca Raton FL June 2017
Naples FL July 2017

Daiichi Sankyo, Inc., Regional & National, multiple
Orlando FL Nov 2017
Boca Raton Nov 2017
Palm Beach Nov 2017
Pembroke Pines Jan 2018
Louisville, KY Feb 2018
Malabar, FL Apr 2018
Birmingham, AL June 2018
Evansville, IN Sept 2018

Bio Delivery Conference, Regional
Fort Lauderdale June 2018

Nevro Conference, Regional & National, multiple
Palm Beach, FL Nov 2017

Las Vegas, NV Jan 2018
Naples, FL June 2018
NY, NY Oct 2018

Professional Memberships: American Society of Anesthesiologists
Florida Society of Anesthesiologists
Society for Pain Practice Management
American Academy of Pain Management
American Society of Addiction Medicine

- Board Certified in Anesthesiology, 10/96, certification No. 28498
- Board Certified in Pain Medicine, 4/11-4/21, certification No. 12511
- Board Certified in Addiction Medicine, 12/10-12/20, certification No. 2010401
- Board Certified in Preventive Medicine, 1/18-1/28, certification No. 61-1592

Experience testifying as an expert in the past four years:

State of Oklahoma v. Purdue Pharma, L.P., et al., Case No. CJ-2017-816, United States District Court of Cleveland County, State of Oklahoma, March 28, 2019.

Appendix B

Materials Considered

Court Documents

Deposition of Andrew Boyer, *In Re: National Prescription Opiate Litigation*, MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, January 15, 2019.

Deposition of Christine Baeder, *In Re: National Prescription Opiate Litigation*, MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, January 24, 2019.

Deposition of David Cutler, Ph.D., *In Re: National Prescription Opiate Litigation*, MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, April 26, 2019

Deposition of Dr. Russell Portenoy, *State of Oklahoma v. Purdue Pharma, L.P., et al.*, Case No. CJ-2017-816, United States District Court of Cleveland County, State of Oklahoma, January 24, 2019.

Deposition of Mark A. Schumacher, M.D., Ph.D., *In Re: National Prescription Opiate Litigation*, MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, April 23, 2019.

Deposition of Matthew Perri III, *In Re: National Prescription Opiate Litigation*, MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, April 24, 2019.

Deposition of Meredith Rosenthal, *In Re: National Prescription Opiate Litigation*, MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, May 4, 2019.

Deposition of Michael Perfetto, *In Re: National Prescription Opiate Litigation*, MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, December 18, 2018.

Expert Report of Anna Lembke, M.D., *In Re National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019.

Expert Report of Professor Meredith Rosenthal, *In Re National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019.

Expert Report of David S. Egilman, M.D., MPH, *In Re National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019.

Expert Report of David Kessler, M.D., *In Re National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019.

Expert Report of Katherine Keyes, Ph.D, MPH, *In Re National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019.

Expert Report of Ted Miller, Ph.D., *In Re National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019.

Expert Report of Matthew Perri III, *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019.

Expert Report of Mark A. Schumacher, M.D., Ph.D., *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019.

Expert Report of Scott L. Wexelblatt, M.D., *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019.

Summit County, Cuyahoga County, and the Cities of Akron and Cleveland, Ohio Plaintiffs' Responses and Objections to Manufacturer Defendants' Fourth Set of Interrogatories, *In Re: National Prescription Opiate Litigation*, Case No. 17-md-2804, United States District Court for the Northern District of Ohio Eastern Division.

Third Amended Corrected Complaint, *In Re: National Prescription Opiate Litigation*, May 29, 2018

Bates-Stamped Documents

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"Actiq TIRF REMS Documentation," TEVA_MDL_A_00709777-10056.

"Fentora Marketing Materials," TEVA_MDL_A_00025238-33471.

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